PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 417/06, A61K 31/41, 31/425

A1

(11) International Publication Number: **WO 99/45008**

(43) International Publication Date: 10 September 1999 (10.09.99)

(21) International Application Number: PCT/EP99/01327

(22) International Filing Date: 1 March 1999 (01.03.99)

(30) Priority Data:

98104036.3	6 March 1998 (06.03.98)	EP
98123310.9	8 December 1998 (08.12.98)	EP
99101360.8	26 January 1999 (26.01.99)	EP

(71) Applicant: F. HOFFMANN–LA ROCHE AG [CH/CH]; Grenzacherstrasse 124, CH–4070 Basle (CH).

(72) Inventors: HAYASE, Tadakatsu; Nippon Roche Syonanryo A–103, Higashikaiagan–Minami 6–6–17, Chigasaki–shi, Kanagawa–ken 253–0054 (JP). ICHIHARA, Shigeyasu; Kizuki 1620, Nakahara–ku, Kawasaki–shi, Kanagawa–ken 221–0025 (JP). ISSHIKI, Yoshiaki; Nippon Roche Syonanryo A–107, Higashikaigan–Minami 6–6–17, Chigasaki–shi, Kanagawa–ken 253–0054 (JP). LIU, Pingli; 303, 7–10–26, Zengyo, Fujisawa–shi, Kanagawa–ken 251–0033 (JP). OHWADA, Jun; Kamakura Ueki Urban Life Rm 403, Ueki 484–3, Kamakura–shi, Kanagawa–ken 247–0073 (JP). SAKAI, Toshiya; 2–14–4 Kataseyama, Fujisawa–shi, Kanagawa–ken 251–0033 (JP). SHIMMA, Nobuo; Higashikaigan–Minami 2–11–19, Chigasaki–shi, Kanagawa–ken 253–0054 (JP). TSUKAZAKI, Masao; Corbusier Syonandai Rm 202, Engyo 1–18–5, Fujisawa–shi, Kanagawa–ken 252–0805 (JP). UMEDA, Isao; Imperial Higashihakuraku Gardenhouse Rm B–513, Shirahataminami–cho 1–1, Kanagawa–ku, Yokohama–shi, Kanagawa–ken 221–0073 (JP). YAMAZAKI, Toshikazu; Sunaoshisou 22, 2–2–11 Kobukuroya, Kamakura–shi, Kanagawa–ken 247–0055 (JP).

(74) Agent: MAHE, Jean; Grenzacherstrasse 124, CH–4070 Basle (CH).

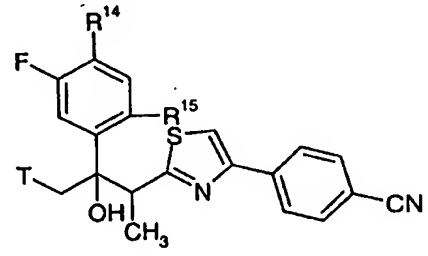
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

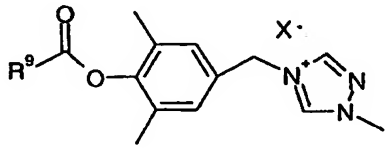
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

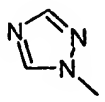
(54) Title: 3–[4–(4–CYANOPHENYL)THIAZOL–2–Y)]–1–(1H–1,2,4–TRIAZOL–1–YL)–BUTAN–2–OL DERIVATIVES HAVING ANTIFUNGAL ACTIVITY



(I)



(T1)



(T2)

(57) Abstract

Azole derivatives of formula (I) wherein R^{14}, R^{15} are each independently hydrogen or fluorine, T is a group of formula (T^1) or (T^2), wherein R^9 is pyrrolidinyl or a group A–NH–B–, A is hydrogen or straight–chain or branched C_1–C_5 alkyl; B is straight–chain or branched C_1–C_4 alkylene, $-CH_2-CONH-CH_2$ or $-CH_2CH_2CH_2-CH(NH_2)$; and X is a pharmaceutically acceptable anion; and pharmaceutically acceptable salts of said compounds, and hydrates and solvates of the compounds of formula (I) and the salts thereof can be used in the production of medicaments for treating fungal infections and mycoses.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

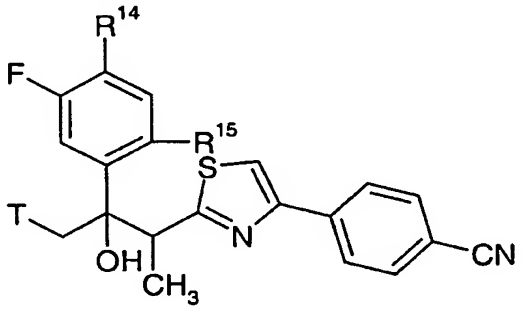
AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**R**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

3-[4-(4-CYANOPHENYL)THIAZOL-2-Y)]-1-(1H-1,2,4-TRIAZOL-1-YL)-BUTAN-2-OL DERIVATIVES HAVING ANTIFUNGAL ACTIVITY

The present invention relates to novel azoles, processes for their manufacture, pharmaceutical, particularly antifungal compositions containing said azoles, and the use of these azoles for the production of medicaments for the therapy of fungal infections.

Several azoles are currently used for systemic mycoses. However, none of them fulfills the needs of clinical requirement in full extent, particularly with regard to broad antifungal spectrum including aspergillus fumigatus, less drug-drug interaction, and appropriate plasma half-life for once a day treatment. Other clinical requirements which are not fulfilled by the azoles currently used, are efficacy against major systemic mycoses including disseminated aspergillosis, safety, and oral or parenteral formulations. Particularly, demand of a parenteral administration of the azoles is increasing for the treatment of serious systemic mycoses. Most of the azoles on the market as well as under development are highly lipophilic molecules that make the parenteral formulation difficult.

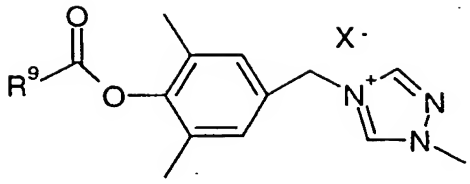
The novel azoles of the present invention have the formula



I

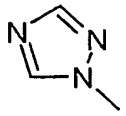
wherein R^{14}, R^{15} are each independently hydrogen or fluorine,

T is a group of the formula:



(T¹)

or



(T²)

wherein

R^9 is pyrrolidinyl or a group A-NH-B-,

A is hydrogen or straight-chain or branched C_1-C_5 alkyl;

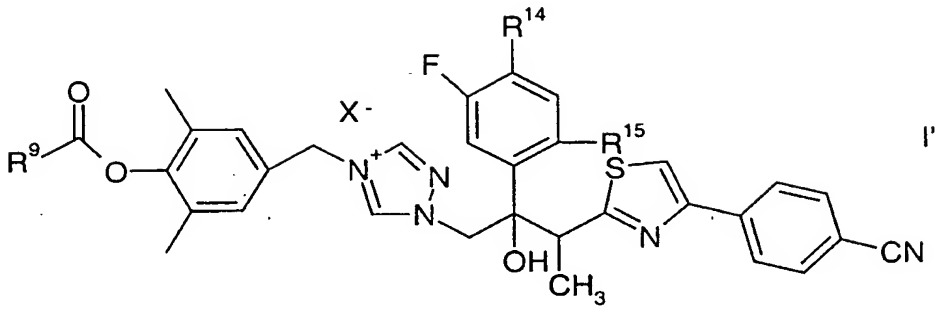
B is straight-chain or branched C_1-C_4 alkylene, $-CH_2-CONH-CH_2$ or $-CH_2CH_2CH_2-CH(NH_2)$; and

X^- is a pharmaceutically acceptable anion;

and pharmaceutically acceptable salts of said compounds, and hydrates and solvates of the compounds of formula I and the salts thereof.

The novel azoles of the above formula I have less metabolic interaction liability which is a clear clinical advantage. Those azoles of formula I, wherein T is a group T^1, are water soluble compounds useful for the treatment of systemic mycoses and suitable for both oral and particularly parenteral administration. Thus, the invention also relates to a method for the therapy of fungal infections and mycoses, which comprises administering to the infected organism an effective amount of the novel azole compounds.

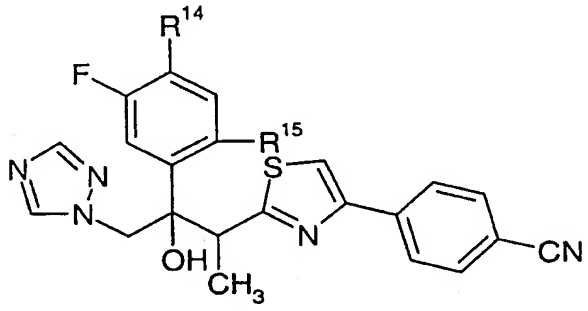
Where T is T^1 in the above formula I, the azoles of the invention have the formula



I'

wherein R^9, R^{14} and R^{15} are as above.

Where T is T^2 in the above formula I, the azoles of the invention have the formula



II

wherein R^{14} and R^{15} are as above.

Preferred compounds of formula I (I' or II) are those wherein R^{14}=R^{15}=H or F, or R^{14} is H and R^{15} is F.

Also preferred among the compounds of formula I' are those wherein R^9 is 2-pyrrolidinyl, aminomethyl, (methylamino)methyl or (ethylamino)methyl.

The anion X^- can be derived from a pharmaceutically acceptable inorganic acid, and thus is a chloride, bromide, sulfate or the like. The anion X^- can also be derived from an organic acid, e.g. an aliphatic, aromatic or araliphatic carboxylic acid or sulfonic acid, and thus is an

acetoxy, trifluoroacetoxy, mesyloxy or the like anion.

Examples of preferred azole compounds of the formula (I') are:

1-[(2R,3R)-3-[4-(4-cyanophenyl)-thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[(S)-3,5-dimethyl-4-(pyrrolidine-2-carbonyloxy)-benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)-thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[(S)-3,5-dimethyl-4-(pyrrolidine-2-carbonyloxy)-benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-[4-cyanophenyl)thiazol-2-yl)]-2-(3-fluorophenyl)-2-hydroxybutyl]-3-[(S)-3,5-dimethyl-4-(pyrrolidine-2-carbonyloxy)-benzyl]-1H-1,2,4-triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

(2R,3R)-4-(4-aminoacetoxy-3,5-dimethylbenzyl)-1-[3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

(2R,3R)-4-(4-aminoacetoxy-3,5-dimethylbenzyl)-1-[3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

(2R,3R)-4-(4-aminoacetoxy-3,5-dimethylbenzyl)-1-[3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide, and

particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

(2R,3R)-1-[3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[4-[(ethylamino)-acetoxy]-3,5-dimethylbenzyl]-1H- [1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

(2R,3R)-1-[3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[4-[(ethylamino)-acetoxy]-3,5-dimethylbenzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(ethylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)-acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium chloride, and particularly its hydrochloric acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]-benzyl]-1H-[1,2,4]triazol-4-ium chloride, and particularly its hydrochloric acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium chloride, and particularly its hydrochloric acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]-benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrobromic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]-benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrobromic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrobromic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]-benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrochloric acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]-benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrochloric acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrochloric acid salt.

Examples of preferred triazole compounds of the formula (II) are:

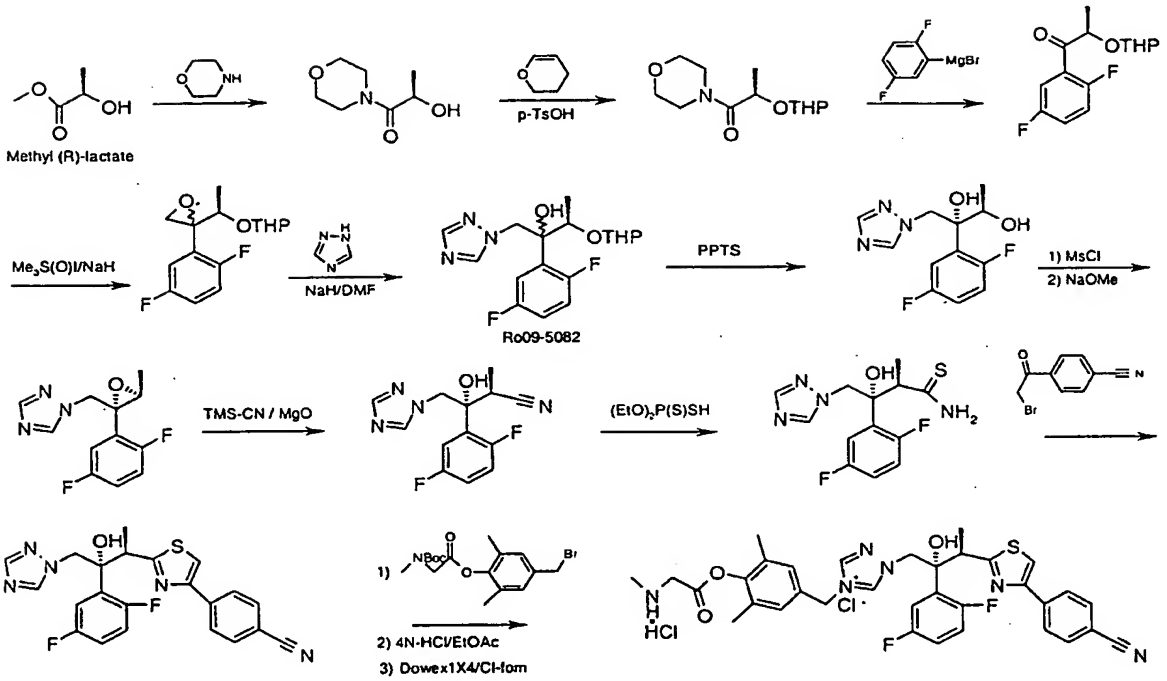
(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-1-(1H-1,2,4-triazol-1-yl)-2-(2,4,5-trifluorophenyl)-butan-2-ol,

(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol,

(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(3-fluorophenyl)-1-(1H-1,2,4-triazole-1-yl)-butan-2-ol.

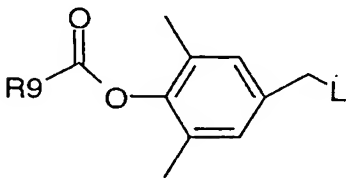
The following synthetic scheme 1 illustrates the manufacture of one of the compounds of formula I':

Synthetic scheme 1.



5

The novel azole compounds represented by the general formula I' as well as salts, hydrates or solvates thereof can be manufactured by reacting an azole compound of the above general formula (II) with a compound of the general formula (III),



(III)

wherein R^9 is the same as defined above, and an amino group present in R^9 may be in protected form; and L is a leaving group,

followed if necessary, by removal of a protecting group and/or by salt formation.

The benzylation reactions of the compound of the general formula (II) with the compound of the general formula (III) can be carried out in a solvent such as methylene chloride, chloroform, benzene, toluene, acetonitrile, tetrahydrofuran, dioxane, or dimethylformamide, preferably chloroform, acetonitrile, or dimethylformamide. The reaction time of this benzylation reaction may be varied within a relatively wide range. In general, the reaction can be carried out at a temperature between 0°C and 100°C, preferably between 0°C and 50°C. Preferably, an amino group present in R^9 in the compound of formula III is protected by a suitable amino protecting group, such as tert.-butoxycarbonyl. The protecting group may, if necessary, be removed after the reaction by procedures known to those skilled in the art.

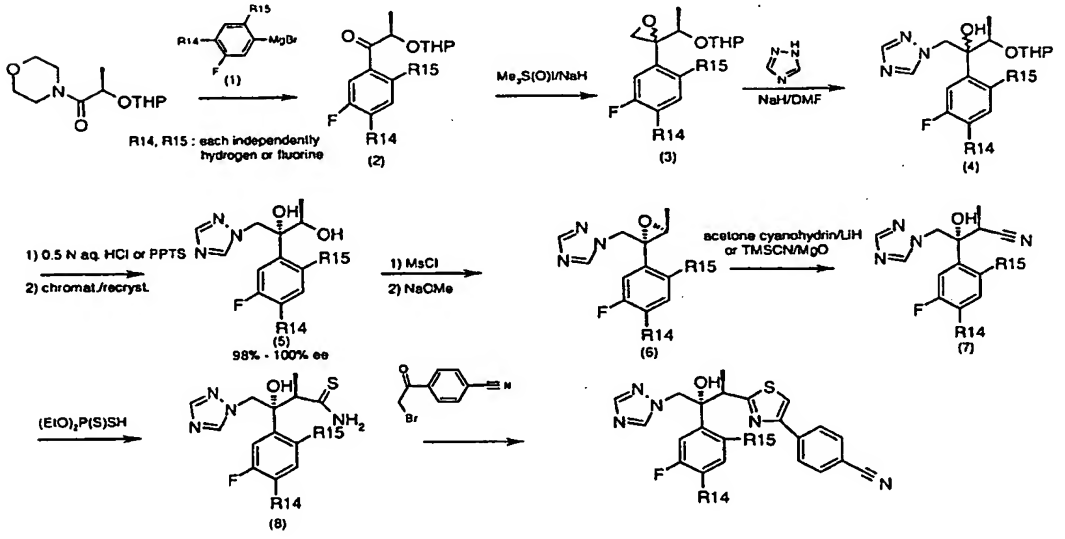
The compounds of formula (I') may contain an amino acid ester substituent R^9 which substituents may form acid addition salts. The

term "salts of compounds of formula (I)" in the present specification, refers to such acid addition salts. These salts may be derived from pharmaceutically acceptable acids as described earlier with reference to the symbol X^-. The salt formation can be performed when removing a protecting group, or can be performed ad hoc by procedures known per se.

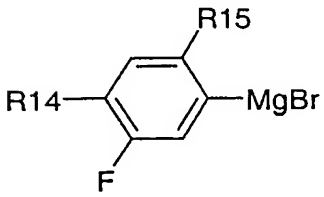
The hydration can be effected in the course of the manufacturing process or can occur gradually as a result of hygroscopic properties of an initially anhydrous product. Solvates with pharmaceutically acceptable solvents such as ethanol can be obtained for example, during crystallization.

The azoles of formula (II) as well as salts, hydrates or solvates thereof can be manufactured according to the following synthetic scheme 2, starting from 4-[(2R)-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)propionyl]morpholine [which can be prepared by a same procedure as described in Chem. Pharm. Bull. 41, 1035, 1993.].

Synthetic scheme 2.



(a) Reacting 4-[(2R)-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)propionyl] morpholine with a compound of the formula (1) in an organic solvent such as tetrahydrofuran (THF) at a temperature between –10°C and room temperature for 3 to 8 hr. to give a compound of the formula (2),

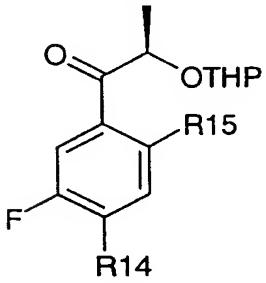


(1)

in which R^{14} and R^{15} are each independently hydrogen or fluorine atom (hereinafter R^{14} and R^{15} have the same meaning),

followed by

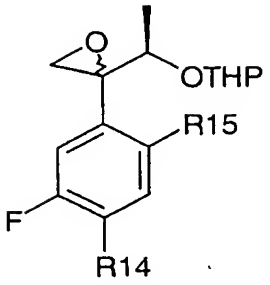
(b) reacting a compound of the formula (2) with trimethyl sulfoxonium iodide, in the presence of sodium hydride in THF and dimethyl sulfoxide (DMSO) or in the presence of BuLi in THF and N,N'-dimethylpropylene urea (DMPU), at a temperature between -5°C and room temperature for 2 to 8 hr. to give a compound of the formula (3),



(2)

followed by

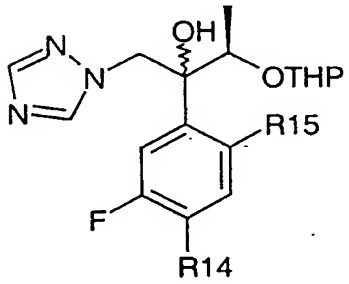
(c) reacting a compound of the formula (3) with triazole in the presence of sodium hydride in dry dimethylformamide (DMF) at a temperature between 50°C and 100°C for 6 to 12 hr. to give a compound of the formula (4),



(3)

followed by

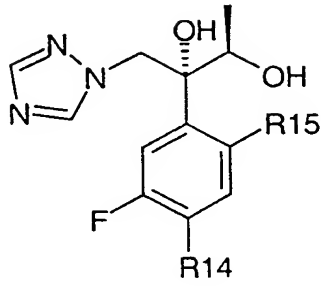
(d) reacting a compound of the formula (4) with aqueous hydrochloric acid at a concentration between 1N and 0.1N solution, in methanol and n-hexane at room temperature or pyridinium p-toluenesulfonate in ethanol, at a temperature between room temperature and 100°C for 2 to 6 hr. The resulting compound is recrystalized from t-butyl methyl ether and n-hexane to give a compound of the formula (5),



(4)

followed by

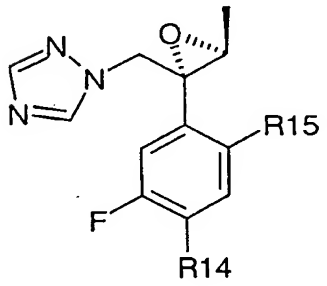
(e) reacting a compound of the formula (5) with mesyl chloride in CH_2Cl_2 and methyl acetate (AcOEt) in the presence of an organic base such as triethylamine or pyridine for 30 min. to 2 hr. This reaction is followed by epoxy ring formation with sodium methoxide in methanol for 15 min. to 1 hr. The resulting compound is purified by recrystalization from t-butyl methyl ether and n-hexane or by silicagel column chromatography using CH_2Cl_2 and methanol as eluent, to give a compound of the formula (6),



(5)

followed by

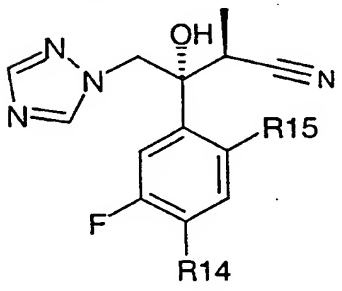
(f) reacting a compound of the formula (6) with acetone cyanohydrin in the presence of lithium hydride in THF under reflux for 4 to 8 hr.or trimetylsilyl cyanide in the presence of magnesium oxide in o-xylene at a temperature between 100°C and 160°C for 20 to 40 hr, then removing of trimethylsilyl group with conc. hydrogen chloride solution in THF to give a compound of the formula (7),



(6)

followed by

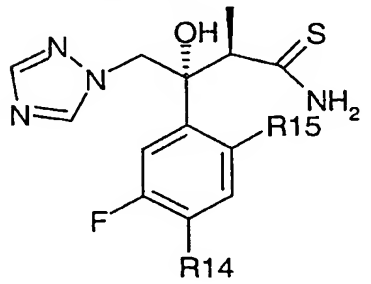
(g) reacting a compound of the formula (7) with dithiophosphoric acid O,O-diethyl ester and water or dithiophosphoric acid O,O-diethyl ester, water and iso-propanol at a temperature between 90°C and 150°C for 4 to 8 hr. to give a compound of the formula (8),



(7)

followed by

(h) reacting a compound of the formula (8) with 2-bromo-4'-cyanoacetophenone at a temperature between room temperature and 80°C in acetonitrile, ethanol or methanol for 2 to 24 hr. to give a compound of the formula (II),



(8)

The azoles of formulae I' and II with a configuration other than 2R,3R can be synthetized in a way similar to that described above.

The term "salts of compounds of the formula (II)" in the present specification refers to acid addition salts. These salts may be derived from pharmaceutically acceptable acids such as acetic acid and hydrogen chloride.

The salt formation can be performed ad hoc by procedures known per se. Hydrates or solvates with pharmaceutically acceptable solvents such as ethanol can be obtained for example, during crystallization.

Fungal infections usually occur in immunocompromised patients with underlying diseases. Antifungal agents are, therefore, often taken with other medications. When co-administered with other drugs, azole antifungals have been reported to increase the blood concentrations of some of the drugs administered concomitantly. Such drug-drug interactions can sometimes result in severe adverse effects and sometimes form a basis for contraindication. This is one of critical issues of azole antifungals such as itraconazole, fluconazole and ketoconazole. The novel azoles represented by the formula (II) as well as hydrates or solvates thereof have less drug-drug interaction than known antimycotic azole compounds (see Table 1). Therefore, these azoles would have a clear clinical advantage.

In vitro P450 inhibitory activity

Each azole compound at different concentrations was incubated with a specific substrate for each CYP, human liver microsomes and NADPH at 37°C. Then, the metabolite formed from the specific substrate was determined by HPLC

and the 50% inhibitory concentration (IC_{50}) was calculated. The substrate concentrations and incubation conditions were as follows:

(1) substrate for CYP3A4: midazolam (10 μM), formation of 1-hydroxymidazolam after incubation for 10 min at 37 .

(2) substrate for CYP2C9: tolbutamide (100 μM), formation of 4-hydroxytolbutamide after incubation for 10 min at 37 .

Table 1

In vitro inhibitory activity of azole antifungals against Cytochrome P450 isozymes using human liver microsomes

	P450 inhibition IC50 (μM)	
	CYP 3A4(1)	CYP 2C9(2)
Ketoconazole	0.19	13.9
Itraconazole	0.36	25.7
Fluconazole	50	> 50
Example 5	23	18.4
Example 4	4.1	35.1

In vitro antifungal activities

The *in vitro* antifungal activities were evaluated by determining the 80 % inhibitory concentration (IC_{80}), which were calculated as the lowest concentration of an antifungal to inhibit the growth of fungus to 20 % turbidity compared with the drug-free control growth spectrophotometrically.

The IC_{80} values were determined by the broth micro-dilution procedure based on NCCLS Approved Standard [National Committee for Clinical Laboratory Standards (1997). Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved standard. Document M27-A] with the following minor modification: RPMI1640 medium used for filamentous fungi was solidified with 0.2% low melting point agarose (BRL).

In vitro antifungal spectrum of the azole compounds of the present invention are shown in Table 2.

Table 2 Geometric mean of IC_{80} of Azoles against reference strains

	n=	Fluconazole	Itraconazole	Example 4
C.albicans	3	0.87 (0.31-6)	0.008 (0.059)	0.014 (0.0054-0.082)
C.glabrata	2	5.2 (5-5.4)	0.078 (0.041-0.059)	0.090 (0.051-0.16)
C.guilliermondii	2	2.3 (1.9-2.9)	0.032 (0.022-0.047)	0.071 (0.053-0.094)
C.tropicalis	2	0.59 (0.25-1.4)	0.35 (0.0054-23)	0.33 (0.019-2.7)
C.krusei	2	25 (19-33)	0.038 (0.023-0.064)	0.11 (0.069-0.19)
C.parapsilosis	2	1.6 (1.0-2.5)	0.017 (0.017)	0.025 (0.02-0.32)
C.lusitaniae	2	0.18 (0.1-0.32)	0.0021 (0.0014-0.0031)	0.0051 (0.0027-0.0095)
C.neoformans	2	3.7 (3.1-4.3)	0.015 (0.012-0.018)	0.042 (0.042-0.068)
A.fumigatus	10	>88 (45->100)	0.027 (0.012-0.086)	0.11 (0.060-0.28)
F.solani	6	>100 (>100)	47 (17->100)	11 (4.0-23)
F.moniliforme	2	>100 (>100)	4.3 (0.021-0.69)	1.8 (1.2-2.8)
A.corymbifera	5	>100 (>100)	0.053 (0.021-0.078)	0.37 (0.18-1.3)
R.pusillus	3	>90 (90->100)	0.19 (0.012-33)	0.68 (0.24-3.1)
R.oryzae	4	>100 (>100)	0.18 (0.045-2.2)	0.59 (0.18-2.9)
R.microsporus	3	>100 (>100)	0.29 (0.19-0.33)	1.1 (0.59-0.69)
C.bertholletiae	2	>100 (>100)	0.22 (0.15-0.33)	5.9 (5.9)

Therefore, the triazole compounds of the formula (II) as well as salts,

hydrates or solvates thereof, according to the present invention, exhibit potent antifungal activity against various fungal infections including Aspergillosis in mice over a very wide range of dosages both orally and parenterally and are useful as antifungal agents.

The novel azole compounds represented by the general formula (I') as well as hydrates or solvates thereof have high water solubility particularly in comparison to known antimycotic azole compounds. The solubility of two products of the invention is given in Table 3.

Table 3

Compound (Example No.)	solubility in distilled water (mg/ml)
1	22
3	>7

In addition, the azole of formula I' are chemically stable in aqueous solution at room temperature more than three days, but are efficiently converted into compounds of formula (II) in either mouse, rat, monkey or human plasma. The conversion of representatives of the new azole compounds of the general formula (I') to compounds of formula (II) in human plasma are shown in Table 4. The compounds of formula (I') were incubated with human plasma at a concentration of 10µg/ml at 37°C for up to 20 min.

Table 4. Conversion of compounds of formula (I') to compounds of formula (II) in human plasma

Example No.	Conversion half-life (min)	Incubation time (min)	Observed (%)	
			Comp. (I')	Compound(II)
1	< 1	5	< 5	96
3	< 1	5	< 5	89

In vivo efficacy of the compounds of the present invention is shown in Table 5. Male Fisher rats, strain F344/DuCrj, were employed for experimental infection models such as systemic candidiasis, systemic aspergillosis and pulmonary aspergillosis model. Immunocompetent 4 weeks old rats were used for systemic candidiasis or systemic aspergillosis which occurred after infection with Candida albicans conidia of $5x10^6$/rat or with Aspergillus fumigatus conidia of $6x10^5$/rat via tail vein. Otherwise, for pulmonary aspergillosis model, rats had been immunosuppressed by cortisone acetate treatments prior to infection with $2x10^5$/rat intratrachially. Treatments were given twice on the first day, and once daily on the following 4 days, both for systemic and pulmonary aspergillosis. For systemic candidiasis rats were treated at 0, 4, 24, and 48 h after infection. Effective dose 50% (ED^{50}) values were determined on day 14 after infection.

Table 5

(μmol/kg)

	Systemic candidiasis		Pulmonay aspergillosis		Systemic aspergillosis	
				i.v.		i.v.
	iv.	p.o.	p.o.		p.o.	
Example 1	5.3	5.3	7.4±3.8	8.0±4.2	5.8	3.0
Itraconazole	n.t.	3.9±2.2	n.t.	2.0±1.1	n.t.	4.0
Fluconazole	n.t.	1.4	n.t.	n.t.	n.t.	n.t.

Therefore, the water soluble compounds of the general formula (I') as well as the salts, hydrates or solvates thereof exhibit potent activity against various fungal infections including Aspergillosis in rats over a very wide range of dosages both orally and parenterally and are useful as antifungal agents.

The present invention further relates to the pharmaceutical compositions containing an azole compound of the general formula I or a salt, hydrate or solvate thereof.

The azole compounds of the formula I as well as salts, hydrates or solvates thereof are very active antimycotic agents. They are active against a variety of fungal species including *Candida spp.*, *Cryptotoccus neoformans*, *Aspergillus spp.*, *Trichophyton* spp., *Microsporum* spp., *Exophiala* spp., *Blastomyces dermatitidis*, and *Histoplasma capsulatum*. Thus, the compounds of the present invention are useful for topical and systemic treatment of mycoses in animals as well as in humans. For example, they are useful in treating topical and mucosal fungal infections caused by, among other genera, *Candida*, *Trichophyton*, or *Microsporum*. They may also be used in the treatment of systemic fungal infections caused by, for example, *Candida spp.*, *Cryptococcus*

neoformans, *Aspergillus spp.*, *Paracoccidiodes spp.*, *Sporotrix spp.*, *Exophiala spp.*, *Blastomyces spp.*, or *Histoplasma spp.*.

For clinical use, the azole compound of the formula I as well as salts, hydrates or solvates thereof can be administered alone, but will generally be administered in pharmaceutical admixture formulated as appropriate to the particular use and purpose desired, by mixing excipient, binding agent, lubricant, disintegrating agent, coating material, emulsifier, suspending agent, solvent, stabilizer, absorption enhancer and/or ointment base. The admixture can be used for oral, injectable, rectal or topical administration. Pharmaceutical formulation for oral administration may be granule, tablet, sugar coated tablet, capsule, pill, suspension or emulsion. For parenteral injection, for example, intravenously, intramuscularly or subcutaneously, the azoles of formula I may be used in the form of a sterile aqueous solution or in the form of a HPCD complex, which may contain other substances, for example, salts or glucose to make the solution isotonic. The azoles can also be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder.

The daily dosage level of the azole compounds of the formula I is from about 0.1 to about 50 mg/kg (in divided doses) when administered in one, two or more dosages by either the oral or parenteral route. Thus, tablets or capsules may contain from about 5 mg to about 0.5 g of active compound for administration. In any event the actual dosage can be determined by the physician and it may be varied upon the age, weight and response of the particular patient.

In addition, the azole compounds of the formula I as well as salts, hydrates or solvates thereof have activity against a variety of plant

pathogenic fungi, including for example *Pyricularia oryzae*, *Pythium aphanidermatum*, *Alternaria* spp., and *Paecilomyces variotii*. Thus, they can be applied for agricultural and horticultural purposes preferably in the form of a composition formulated as appropriate to the particular use and purpose desired, for example dusting powders, or granules, seed dressings, aqueous solutions, dispersions or emulsions, dips, sprays or aerosols. Such compositions may contain such conventional carriers, diluents or adjuvants as are known and acceptable in agriculture and horticulture. Other compounds having herbicidal or insecticidal, or additional antifungals can be incorporated in the compositions. The compounds and compositions can be applied in a number of ways, for example they can be applied directly to the plant foliage, stems, branches, seeds or roots or to the soil or other growing medium, and they may be used not only to eradicate the disease, but also prophylactically to protect the plants or seeds from attack.

The following examples merely illustrate the preferred methods for the preparation of the compounds of the present invention and are not intended to limit the scope of the invention thereto.

Example 1

a) Preparation of (2R)-2',5'-Difluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-propiophenone

A mixture of magnesium (7.25 g, 0.298 mol) and iodine (catalytic amount) and 1-bromo-2,5-difluorobenzene (20.0 g, 0.178 mol) in THF (250ml) was vigously stirred. The color of iodine was disappeared and the inner temperature rose up to 65°C. To this mixture was added additional 1-bromo-2,5-difluorobenzene (30.0 g, 0.267 mol) dropwise to maintain the inner temperature from 50 to 55°C over 45min. The resulting mixture was stirred at 55°C for 30min. then at r.t. for 1hr. The

mixture was cooled down to -5°C. To this mixture was added a solution of 4-[(2R)-2-(3,4,5,6-Tetrahydro-2H-pyran-2-yloxy)propionyl] morpholine (52.5 g, 0.216 mol) in THF (150ml) dropwise over 40min. And the resulting mixture was stirred at r.t. for 4hrs. The reaction mixture was cooled down to 5°C and saturated NH4Cl aq. (100ml) was added carefully. The whole was diluted with H2O (600ml) and extracted with EtOAc (400ml + 200ml x 2). The combined organic layer was dried over Na2SO4 and concentrated in vacuo. The residue was chromatographed on silica gel (n-hexane : EtOAc = 10 :1 ~ 5 : 1) to give (2R)-2',5'-Difluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-propiophenone (47.3 g, 81 %) as pale yellow syrup.

Physical form : colorless oil; FAB-MS: m/z 271(M+H)$^+$; ^{1}H-NMR($CDCl_3$): 1.42~1.90(9H,m),3.32~3.40(1Hx1/2,m),3.69~3.77(1Hx1/2,m),3.86~3.94 (1Hx1/2,m),4.66(1Hx1/2,t,J=3.6Hz),4.75(1Hx1/2,t,J=3.6Hz),4.87(1Hx1/2, q,J=6.6Hz),5.11(1Hx1/2,q,J=6.9Hz),7.08~7.25(2H,m),7.49~7.55(1H,m).

b) Preparation of 2-(2,5-Difluorophenyl)-2-[(1R)-1-(3,4,5,6,-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane

To a stirred mixture of NaH (60% in oil, 9.1g, 0.228mol) in DMSO (300ml) was added portionwise trimethylsulfoxonium iodide (53.9g, 0.245 mol) at the inner teperature with the range from 15°C to 18°C. over 20min. The ice bath was removed and the mixtuer was stirred at r.t. for 3hrs. The mixture was cooled down to 10°C. To this mixture was added a solution of (2R)-2',5'-Difluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-propiophenone (47.3 g , 0.175 mol) in DMSO (150ml) dropwise over 20min. The resulting mixture was stirred at r.t. for 4hrs. The reaction mixture was poured into ice-water (800ml). The whole was extracted with EtOAc (400ml + 200ml x 2). The combined organic layer was washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was chromatograkkphed on silicagel (n-hexane : EtOAc =

8 : 1 ~ 5 : 1) to give 2-(2,5-Difluorophenyl)-2-[(1R)-1-(3,4,5,6,-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane (48.3 g, 97 %).
Physical form : pale yellow syrup, EI-MS: m/z 284 $(M)^+$; ^{1}H-NMR($CDCl_3$): 1.15(3Hx1/2,dd,J=6.6,1.3Hz), 1.24(3Hx1/2,dd, J=6.6,1.3Hz), 1.52~1.87 (6H,m),2.83~2,90(1H,m),3.07 (1Hx1/2,d,J=5.3Hz),3.36(1Hx1/2,d,J=5.6Hz), 3.48~3.56(1H,m),3.82~3.92 (1H,m),4.00~4.16(1H,m),4.73~4.92(1H,m), 6.96~7.02(1H,m),7.09~7.15 (1H,m).

c) Preparation of (3R)-2-(2,5-difluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a stirred suspension of NaH (60 % in oil, 21.0 g, 0.525 mol) in DMF (300ml) was added portionwise 1,2,4-triazole (43.3 g, 0.627 mol) at the inner temperature from 2°C to 11°C over 30min. The resulting mixture was stirred at r.t. for 1.5hrs. To this mixture was added a solution of 2-(2,5-Difluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane (48.3 g, 0.170 mol) in DMF (50 ml). The mixture was stirred at 60°C for 1hr. and then at 65°C for 14hrs. The reaction mixture was cooled down to 10°C and then poured into ice-water (800 mL). The resulting mixture was extracted with EtOAc (400ml + 200ml x 2). The combined organic layer was dried over Na2SO4 and concentrated in vacuo. The residue was chromatographed on silicagel (n-hexane : EtOAc = 4 : 1 ~ 1 : 5) to give (3R)-2-(2,5-difluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol (43.9 g, 73 %) and recovered starting material (13.2 g, 27 %).
Physical form : colorless syrup ; FAB-MS: m/z 354 $(M+H)^+$; ^{1}H-NMR($CDCl_3$): 1.00(3Hx1/2,d,J=6.6Hz),1.13(3Hx1/2,d,J=6.6Hz), 1.42~1.88(6H,m),3.38~3.60 (1H,m),3.80~4.00(1H,m),4.32~5.02(5H,m),6.83~6.99 (2H,m),7.14~7.21 (1H,m),7.73(1Hx1/2,s),7.74(1Hx1/2,s),7.92(1Hx1/2,s),7.95(1Hx1/2,s).

d) Preparation of (2R,3R)-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol

A mixture of (3R)-2-(2,5-difluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol (43.9 g, 0.124 mol) and PPTS (15.6 g, 62.1 mmol) in EtOH (400ml) was stirred at 55°C for 5hrs. The mixture was was evaporated to remove solvent down to 100ml. The residue was poured into ice-aqueous NaHCO3 (500ml). The whole was extracted with EtOAc (400ml + 200ml x 2). The combined organic layer was dried over Na2SO4 and concentrated in vacuo. The residue was chromatographed on silicagel (CH2Cl2 : MeOH = 20 : 1) to give (2R,3R)-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol (18.0 g, 54 %).

Physical form : colorless syrup ; FAB-MS: m/z 270 $(M+H)^+$; ^{1}H-NMR($CDCl_3$): 0.99(3H,d,J=6.6Hz),2.61(1H,d,J=10.6Hz), 4.31~4.36 (1H,m),4.79,4.88 (2H,ABq,J=14.5Hz),4.84(1H,s),6.84~6.99(2H,m),7.13~7.19(1H,m),7.84(1H,s),7.85(1H,s).

e) Preparation of (2R,3S)-2-(2,5-Difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)-methyl]-oxirane

To a cold (0°C) and stirred solution of (2R,3R)-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol (35.0 g, 0.130 mol) and triethylamine (54.8 ml, 0.393 mol) in CH2Cl2 (500ml) was added a mesylchloride (12.1 ml, 0.156 mol) dropwise over 5min. The resulting mixture was stirred at r.t. for 1.5hrs. The reaction mixture was poured into ice-water (300ml). The resulting mixture was shaken well and the organic layer was separated. The aqueous layer was further extracted with CH2Cl2 (150ml x 2). All the organic layers were combined, dried over Na2SO4 and concentrated in vacuo to give mesylate (46.7 g) as crude syrup. The obtained mesylate was dissolved in MeOH (500ml)

and the solution was cooled down to 0°C. To this solution was added 28% NaOMe methanol solution (29.0 ml). The mixture was stirred at 0°C for 50min. The reaction mixture was evaporated to reduce the volume of the solvent down to 150 ml. The residue was poured into ice-water (300ml). The resulting mixture was extracted with ethylacetate (300ml + 200ml x 2). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was cromatographed on silicagel (hexane : EtOAc = 1 : 3) to give (2R,3S)-2-(2,5-Difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)-methyl]-oxirane (30.3 g, 93 %).

Physical form : white solid ; FAB-MS : m/z 252 $(M+H)^+$; ^{1}H-NMR($CDCl_3$): 1.64(3H,d,J=5.6Hz),3.19(1H,q,J=5.6Hz),4.42,4.97 (2H,ABq,J=14.8Hz), 6.75~6.81(1H,m),6.89~7.01(2H,m),7.83(1H,s),7.98 (1H,s).

f) Preparation of (2S,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyronitrile

A mixture of (2R,3S)-2-(2,5-Difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)-methyl]-oxirane (30.3 g, 0.121 mol), trimethylsilylcyanide (65.0 ml) and MgO (24.5 g) in o-xylene (400 ml) was stirred at 130°C for 10hrs. To this mixture was added additional trimethylsilylcyanide (20.0 ml) and MgO (8.5 g) and the resulting mixture was stirred at 130°C further for 6hrs. The reaction mixture was cooled down to r.t. The precipitate was filtered off and washed with CH2Cl2. The filtrate was concentrated in vacuo to give crude brown syrup.

This crude syrup was dissolved in THF (600ml) and the solution was cooled down to 0°C. To this mixture was added 1.0 M tetra n-butylammoniumfluoride THF solution (133ml, 0.133 mol) dropwise over 5min. The mixture was stirred at r.t. for 50min. The solvent was removed under reduced pressure down to 150ml. The residue was poured into ice-water (400ml). The resulting mixture was extracted

with EtOAc (300ml + 200ml x 2). The combined organic layer was dried over Na2SO4 and concentrated in vacuo. The residue was chromatographed on silicagel (n-hexane : EtOAc = 1 : 3) to give (2S,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyronitrile (30.5 g, 91 %).

Physical form : colorless syrup ; FAB-MS : m/z 279 $(M+H)^+$; ^{1}H-NMR($CDCl_3$): 1.19(3H,d,J=7.3Hz),3.33(1H,q,J=7.3Hz),4.82,5.00 (2H,ABq,J=13.9Hz), 5.56(1H,brs),6.89~7.04(2H,m),7.12~7.19(1H,m),7.85(1H,s),7.86(1H,s).

g) **Preparation of (2R,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-ylthiobutyramide**

A mixture of (2S,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyronitrile (30.5 g, 0.110mol), diethyldithio-phospate (235 ml) and H2O (110 ml) was stirre at 80°C for 2hrs. The reaction mixture was cooled down to r.t. n-Hexane (400ml) and water (200 ml) was added. The whole was shaken well and the aqueous layer was separated. The remaining organic layer was further extracted with H2O (100ml x 3). All the aqueous layer was combined. Cooled down to 0°C and neutralized and basified (PH8) with NaHCO3. This basic(PH8) aqueous layer was extracted with EtOAc (300ml + 100ml x 3). The combined organic layer was dried over Na2SO4 and concentrated in vacuo to give dark brown syrup. By addition of CH2Cl2 (100ml) to this crude syrup, precipitate was formed. The precipitate was filtered and washed with CH2Cl2-hexane (5 : 1 mixture) to give (2R,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-ylthiobutyramide (19.2 g, 56 %) as white powder. On the oter hand, the filtrate was concentrated in vacuo and the residue was chromatographed on silica gel (Wako-gel C-300, CH2Cl2 : MeOH = 20 : 1) to give additional (2R,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-

methyl-4-[1,2,4]triazol-1-ylthiobutyramide (7.46 g, 22 %) as pale brown amorphous powder.

Physical form : White solid ; FAB-MS : m/z 313 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$): 1.12(3H,d,J=7.3Hz),3.74(1H,q,J=7.3Hz), 4.55,5.12 (2H,ABq,J=14.5Hz), 5.84(1H,s),6.85~7.02(2H,m),7.15~7.22(1H,m),7.80 (1H,s),7.89(1H,s), 7.89(1H,brs),8.43(1H,brs).

h) Preparation of 4-{2-[(1R,2R)-2-(2,5-Difluoro-phenyl)-2-hydroxy-1-methyl-3-[1,2,4]triazol-1-yl-propyl]-thiazol-4-yl}-benzonitrile

A mixture of (2R,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-ylthiobutyramide (26.7 g, 85.4 mmol) and a-bromo-4'-cyano-acetophenone (24.0 g, 0.107 mol) in EtOH (500ml) was refluxed for 1hr. The reaction mixture was cooled down to r.t. And the solvent was removed under reduced pressure down to 150ml. The residue was poured into in to cold (0°C) saturated NaHCO3 aq. (400ml). The resulting mixture was extracted with EtOAc (300ml + 150 ml x 2). The combined organic layer was washed with brine (200ml), dried over Na2SO4 and concentrated in vacuo. The residue was chromatographed on silica gel (Wako-gel C-300, Hexane : EtOAc = 1 : 2) to give 4-{2-[(1R,2R)-2-(2,5-Difluoro-phenyl)-2-hydroxy-1-methyl-3-[1,2,4]triazol-1-yl-propyl]-thiazol-4-yl}-benzonitrile (32.0 g, 86 %).

Physical form : colorless heavy syrup ; ESI-MS : m/z 437 $(M)^+$; ^{1}H-NMR($CDCl_3$): 1.25(3H,d,J=7.3Hz),4.12(1H,q,J=7.3Hz),4.26,4.96 (2H,Abq,J=14.5Hz), 5.75(1H,s),6.89~7.07(2H,m),7.23~7.29(1H,m),7.65 (1H,s),7.71(1H,s),7.75,8.02 (4H,Abq,J=8.6Hz),7.85(1H,s).

i) Preparation of 4-{4-[(tert-Butoxycarbonyl-methyl-amino)-acetoxy]-3,5-dimethyl-benzyl}-1-[(2R,3R)-3-[4-(4-cyano-phenyl)-thiazol-2-yl]-2-(2,5-difluoro-phenyl)-2-hydroxy-butyl]-1H-[1,2,4]triazol-4-ium bromide

A mixture of 22.7mg of 4-{2-[(1R,2R)-2-(2,5-Difluoro-phenyl)-2-hydroxy-1-methyl-3-[1,2,4]triazol-1-yl-propyl]-thiazol-4-yl}-benzonitrile and 25.0mg of 4-tert-butoxycarbonyl-methyl-aminoacetoxy-3,5-dimethyl-benzyl bromide in CH_3CN(1.5mL) was refluxed over 15hrs. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel (Wakogel C-200, solvent:CH_2Cl_2/MeOH=10/1) to give 4-{4-[(tert-Butoxycarbonyl-methyl-amino)-acetoxy]-3,5-dimethyl-benzyl}-1-[(2R,3R)-3-[4-(4-cyano-phenyl)-thiazol-2-yl]-2-(2,5-difluoro-phenyl)-2-hydroxy-butyl]-1H-[1,2,4]triazol-4-ium bromide (36.0mg, 84% as colorless heavy syrup) ;

FAB-MS : m/z 743 $(M-Br)^+$; ^{1}H-NMR($CDCl_3$): 1.23(3H,d,J=7.3Hz), 1.47(9H,s),2.14(6H,s),3.03(3H,s),4.15(1H,q,J=7.3Hz),4.25(2H,s), 4.98,5.16(2H,ABq,J=13.9Hz),5.39~5.54(2H,m),6.27(1H,s),6.89~7.07(4H, m),7.24~7.27(1H,m),7.58(1H,s),7.73,8.06(4H,ABq,J=8.58),8.07(1H,s),11.26 (1H,s).

j) Preparation of 1-{(2R,3R)-3-[4-(4-cyano-phenyl)-thiazol-2-yl]-2-(2,5-difluoro-phenyl)-2-hydroxy-butyl}-4-(3,5-dimethyl-4-methylaminoacetoxy-benzyl)-1H-[1,2,4]triazol-4-ium bromide

To a solution of 36mg of 4-{4-[(tert-Butoxycarbonyl-methyl-amino)-acetoxy]-3,5-dimethyl-benzyl}-1-[(2R,3R)-3-[4-(4-cyano-phenyl)-thiazol-2-yl]-2-(2,5-difluoro-phenyl)-2-hydroxy-butyl]-1H-[1,2,4]triazol-4-ium bromide in ethylacetate(2ml) was added dropwise 4N HCl ethylacetate solution(1mL) and the mixture was stirred at r.t. for 4hrs.The precipitate was filtered and washed with diethylether to give 1-{(2R,3R)-3-[4-(4-cyano-phenyl)-thiazol-2-yl]-2-(2,5-difluoro-phenyl)-2-hydroxy-butyl}-4-(3,5-dimethyl-4-methylaminoacetoxy-benzyl)-1H-

[1,2,4]triazol-4-ium bromide (24.5mg, 74% as HCl salt and as white solid) ;

FAB-MS : m/z 643 $(M-Br)^+$; ^{1}H-NMR(DMSO-d): 1.19(3H,d,J=7.3Hz), 2.11(6H,s),2.64(3H,s),4.15(1H,q,J=7.3Hz),4.41(2H,s),4.74,5.04(2H,ABq,J =14.5Hz),5.40(2H,s),6.76(1H,brs),7.10(2H,s),7.20~7.38(2H,m), 7.94,8.21 (4H,ABq,J=8.25),8.45(1H,s),9.07(1H,s),9.50(1H,brs),10.17(1H,s).

Example 2

Preparation of 1-[(2R,3R)-3-[4-(4-Cyanophenyl)thiazol-2-yl]-2-hydroxy-2-(2,5-difluorophenyl)butyl]-4-(3,5-dimethyl-4-methylaminoacetoxybenzyl)-1H-[1,2,4]triazol-4-ium chloride hydrochloride

22.6g of 1-{(2R,3R)-3-[4-(4-cyano-phenyl)-thiazol-2-yl]-2-(2,5-difluoro-phenyl)-2-hydroxy-butyl}-4-(3,5-dimethyl-4-methylaminoacetoxy-benzyl)-1H-[1,2,4]triazol-4-ium bromide was dissolved in 2L of dist. water was shaked for 5h at room temperature with 850g of DOWEX 1x4 (Cl form, 50-100 mesh) and the mixture was filtered and washed with water. The filtrate was lyophilized to obtain 17.9g(84%) of 1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-hydroxy-2-(2,5-difluorophenyl)butyl]-4-(3,5-dimethyl-4-methylaminoacetoxybenzyl)-1H-[1,2,4]triazol-4-ium chloride hydrochloride as a white solid.

FAB-MS : m/z 643 M^+ ; ^{1}H-NMR(DMSO-d): 1.19(3H,d,J=6.9Hz), 2.11(6H,s), 2.63(3H,s), 4.15(1H,q,J=6.9Hz), 4.40(2H,s), 4.75,5.04 (2H,ABq,J=14.2Hz), 5.41(2H,s), 6.86(1H,brs), 7.11(2H,s), 7.20-7.38(2H,m), 7.94,8.20(4H,ABq,J=8.3), 8.45(1H,s), 9.08(1H,s), 9.66(2H,brs), 10.22(1H,s)

Recrystallization of 1.8g of 1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-hydroxy-2-(2,5-difluorophenyl)butyl]-4-(3,5-dimethyl-4-methylamino-acetoxybenzyl)-1H-[1,2,4]triazol-4-ium chloride hydrochloride was done

from 1N-HCl (44mL) to obtain 1.44g (80%) of 1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-hydroxy-2-(2,5-difluorophenyl)butyl]-4-(3,5-dimethyl-4-methylaminoacetoxybenzyl)-1H-[1,2,4]triazol-4-ium chloride hydrochloride as a white crystal.

Example 3

a) **Preparation of 4-[(R)-2-Hydroxypropionyl]morpholine**

A mixture of methyl (R)-lactate (175 g) and morpholine (440 ml, 3 eq) was heated at 85°C for 40 h. The mixture was evaporated under reduced pressure. Purification of the residue by silica gel chromatography (using n-hexane : ethyl acetate = 1:1 ~ ethyl acetate as an eluent) gave 4-[(R)-2-hydroxypropionyl]morpholine (232.4 g, 87 % yield) as a pale yellow oil.

b) **Preparation of 4-[(2R)-2-(3,4,5,6-Tetrahydro-2H-pyran-2-yloxy)propionyl]morpholine**

3,4-Dihydro-2H-pyran (90.5 ml, 1.2 eq) was added dropwise to a mixture of 4-[(R)-2-hydroxypropionyl] morpholine (132 g) and p-toluenesulfonic acid monohydrate (500 mg, 0.003 eq) in dry dichloromethane (500ml) over a period of 15 min with stirring at 0°C. After being stirred for 30 min at 0°C, the mixture was washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification of the residue by silica gel chromatography, using n-hexane : ethyl acetate (8 : 1) ~ ethyl acetate as an eluent, gave 4-[(2R)-2-(3,4,5,6-Tetrahydro-2H-pyran-2-yloxy)propionyl] morpholine (191.6 g, 95 % yield) as a pale yellow oil.

EI-MS(+): m/z 243 (M+)

c) Preparation of (2R)-2',4',5'-Trifluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy) propiophenone

A mixture of magnesium (turnings, 228mg, 1.2eq) and 1-bromo-2,4,5-trifluorobenzene (1.1 ml, 1.2eq) in dry tetrahydrofuran (25 ml) was vigorously stirred for 3h at room temperature until magnesium was completely dissolved. After the mixture was cooled to –10°C, a solution of 4-[(2R)-2-(3,4,5,6-Tetrahydro-2H-pyran-2-yloxy)propinyl]morpholine (1.9g) in dry tetrahydrofuran (5ml) was added dropwise over a period of 5 min. The whole was stirred at r.t. for 24 h. A saturated aqueous solution of ammonium chloride and water were added to the reaction mixture and the resulting mixture was extracted with ethyl acetate. The extracts were combined, washed successively with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure followed by purification of the residue by silica gel chromatography, using n-hexane:ethyl acetate (30:1 ~ 5 : 1) as an eluent, gave (2R)-2',4',5'-Trifluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy) propiophenone (1.8g, 80% yield) as a pale yellow oil. The product was a mixture of 2 diastereomers.

ESI-MS(+) : m/z 289 (MH)+

1H-NMR($CDCl_3$):

1.42-1.90(9H,m), 3.31-3.93(2H,m), 4.62-5.12(2H,m), 6.95-7.05(1H,m), 6.68-7.78(1H,m)

d) Preparation of 2-(2,4,5-Trifluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane

Trimethylsulfoxonium iodide (697mg, 1.2 eq) was added portionwise to a stirred mixture of sodium hydride [60 % mineral oil dispersion]

(122mg, 1.15 eq) and dry dimethyl sulfoxide (7ml) at 0°C. The resulting mixture was stirred at room temperature for 40 min and then cooled in an ice bath. A solution of (2R)-2',4',5'-trifluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)propiophenone (760mg) in dry dimethyl sulfoxide (2 ml) was added to the mixture and stirring was continued for 2 h at room temperature. The mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed successively with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 2-(2,4,5-trifluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane (810mg) as a pale yellow oil, which was a mixture of 4 diastereomers and was used for the next step without further purification.

e) Preparation of (3R)-2-(2,4,5-Trifluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol

1H-1,2,4-Triazole (510mg) was added portionwise to a mixture of sodium hydride [60 % mineral oil dispersion] (264mg) and dry N,N-dimethylformamide (8ml) and the mixture was stirred at room temperature for 35 min. A solution of 2-(2,4,5-trifluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane (796mg) obtained above in dry N,N-dimethylformamide (2ml) was added to the mixture at room temperature. The resulting mixture was heated at 80°C for 1.5h with stirring and after being cooled, the mixture was poured into ice-water and the whole was extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure and purification of the residue by silica gel chromatography, using n-hexane : ethyl acetate (1 : 2) as an eluent, gave (3R)-2-(2,4,5-trifluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol

(760mg, 78 % yield for 2 steps) as a colourless oil. The product was a mixture of 4 diastereomers.

ESI-MS(+) : m/z 372 (MH)+

1H-NMR($CDCl_3$):

1.00-1.35(3H,m), 1.40-1.92(6H,m), 3.39-5.00(7H,m), 6.79-6.91(1H,m), 7.27-7.38(1H,m), 7.74-8.12(2H,m)

f) Preparation of (2R,3R)-2-(2,4,5-Trifluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol

A mixture of (3R)-2-(2,4,5-trifluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol (740mg) and pyridinium p-toluene sulfonate (PPTS ,200mg) in ethanol (15 ml) was heated at 55°C for 7h. The reaction mixture was partitioned between ethyl acetate and water. The water layer was extracted with ethyl acetate.The combined organic extracts were dried over anhydrous magnesium sulfate, and concentrated to dryness in vacuo. Purification of the residue by silica gel chromatography, using dichloromethane : methanol (20 : 1) as an eluent, gave (2R,3R)-2-(2,4,5-trifluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol (361mg, 63 %) as white amorphous.

ESI-MS(+) : m/z 288 (MH)+

1H-NMR($CDCl_3$):

0.99(3H,d,J=6.6Hz), 2.45(1H,br.d), 4.30(1H,m), 4.80(1H,d,J=14.2Hz), 4.84(1H,d,J=14.2Hz), 4.88(1H,s), 6.83-6.93(1H,m), 7.29-7.36(1H,m), 7.87(1H,s), 7.88(1H,s)

g) Preparation of (2R,3S)-2-(2,4,5-Trifluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane

Methanesulfonyl chloride (0.11ml, 1.1 eq) was added to a mixture of (2R,3R)-2-(2,4,5-trifluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol (345mg) and triethylamine (0.2ml) in dry ethyl acetate (2ml) and dry dichloromethane (9 ml) at 0 °C. The mixture was stirred at room temperature for 2h and the reaction mixture was quenched with saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate, and evaporation of the solvent under reduced pressure gave the mesylate as an oil. The resulting oil was dissolved in methanol (10 ml) and sodium methoxide [28 % in methanol] (0.29ml) was added to the mixture at 0°C. The mixture was stirred at 0°C for 30 min and was partitioned between ethyl acetate and water. The organic extract was dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent and purification of the residue by silica gel chromatography, using dichloromethane : methanol (40 : 1) as an eluent, gave (2R,3S)-2-(2,4,5-trifluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (310mg, 96%) as a white solid.

ESI-MS(+) : m/z 270 (MH)+

1H-NMR($CDCl_3$):

1.64(3H,d,J=5.6Hz), 3.19(1H,q,J=5.6Hz), 4.40(1H,d,J=14.5Hz), 4.93(1H,d,J=14.5Hz), 6.85-6.95(2H,m), 7.83(1H,s), 8.02(1H,s)

h) Preparation of (2S,3R)-3-(2,4,5-Trifluorophenyl)-3-hydroxy-2-methyl-4-(1H-1,2,4-triazol-1-yl)butyronitrile

A mixture of 295mg of (2R,3S)-2-(2,4,5-trifluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane, 0.59ml of trimethylsilylcyanide and 222mg of magnesium oxide (light) in 10ml of o-xylene was stirred

at 130°C for 23h. After cooling the mixture was filtered and the filtrate was concentrated to dryness. The resulting oil was dissolved in 10ml of THF and 0.39ml of conc.hydrogen chloride was added to the mixture. The mixture was stirred at room temperature for 22h and was diluted with ethyl acetate and aqueous sodium bicarbonate. The organic extract was dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel chromatography, using dichloromethane : methanol (30 : 1) as an eluent, gave (2S,3R)-3-(2,4,5-trifluorophenyl)-3-hydroxy-2-methyl-4-(1H-1,2,4-triazol-1-yl)butyronitrile (243mg, 75%) as a white solid.

ESI-MS(+) : m/z 297 (MH)+

1H-NMR($CDCl_3$):

1.19(3H,d,J=7.3Hz), 3.27(1H,q,J=7.3Hz), 4.82(1H,d,J=14.2Hz), 4.96(1H,d,J=14.2Hz), 5.60(1H,s), 6.85-6.95(1H,m), 7.29-7.37(1H,m), 7.87(1H,s), 7.88(1H,s)

i) Preparation of (2R,3R)-3-(2,4,5-Trifluorophenyl)-3-hydroxy-2-methyl-4-1H-[1,2,4]triazol-1-yl)thiobutyramide

A mixture of 235mg of (2S,3R)-3-(2,4,5-trifluorophenyl)-3-hydrxy-2-methyl-4-(1H-1,2,4-triazol-1-yl)butyronitrile in 1.5ml of dithiophosphoric acid O,O-diethyl ester and 0.5ml of water was stirred at 100°C for 30min. After cooling, the mixture was washed with n-hexane and the residue was diluted with ethyl acetate and aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel column chromatography, using dichloromethane : methanol (12 : 1) as an eluent, gave (2R,3R)-3-(2,4,5-trifluorophenyl)-3-hydroxy-2-methyl-4-1H-[1,2,4]triazol-1-yl)thiobutyramide (255mg, 98%) as a white amorphous.

ESI-MS(+) : m/z 331 (MH)+

1H-NMR($CDCl_3$):

1.13(3H,d,J=7.3Hz), 3.71(1H,q,J=7.3Hz), 4.54(1H,d,J=14.5Hz), 5.06(1H,d,J=14.5Hz), 5.92(1H,s), 6.83-6.91(1H,m), 7.29-7.38(1H,m), 7.67(1H,br.s), 7.82(1H,s), 7.88(1H,s), 8.30(1H,br.s)

j) Preparation of 2-Bromo-4'-cyanoacetophenone

To a mixture of para-cyanoacetophenone (52g, 0.36mol) in chloroform (520ml) and 48%HBr (5.2ml), a solution of bromine (19.3ml) in chloroform (52ml) was added dropwise over a period of 20min. The mixture was stirred for 3h at room temperature and neutralized to pH7 with sat. NaHCO3. The organic layer was washed with sat. NaCl and dried over anhydrous Na2SO4 and concentrated. The residue was chromatographed on silica gel (AcOEt / n-hexane = 1/3 as an eluent) and recrystallized to obtain 2-bromo-4'-cyanoacetophenone as a colourless plate (23.4g, 29%).

EI-MS(+) : m/z 223 (M+)

1H-NMR($CDCl_3$):

4.43(2H,s), 7.80(2H,d,J=6.6Hz), 8.09(2H,d,J=6.6Hz)

k) Preparation of (1R,2R)-4-[2-[2-Hydroxy-1-methyl-3-[1,2,4]triazol-1-yl-2-(2,4,5-trifluorophenyl)propyl]thiazol-4-yl]benzonitrile

A mixture of 188mg of (2R,3R)-3-(2,4,5-trifluorophenyl)-3-hydroxy-2-methyl-4-1H-[1,2,4]triazol-1-yl)thiobutyramide and 141mg of 2-bromo-4'-cyanoacetophenone in 4ml of acetonitrile was stirred for 22h at room temperature. The mixture was diluted with ethyl acetate and was

washed with aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel column chromatography, using dichloromethane : ethyl acetate (3 : 1) as an eluent, gave (1R,2R)-4-[2-[2-hydroxy-1-methyl-3-[1,2,4]triazol-1-yl-2-(2,4,5-trifluorophenyl)propyl]thiazol-4-yl]benzonitrile (212mg, 82%) as a white solid.

ESI-MS(+) : m/z 456 (MH)+

1H-NMR($CDCl_3$):

1.25(3H,d,J=7.3Hz), 4.08(1H,q,J=7.3Hz), 4.25(1H,d,J=14.2Hz), 4.91(1H,d,J=14.2Hz), 5.88(1H,s), 6.89-6.99(1H,m), 7.35-7.45(1H,m), 7.65(1H,s), 7.71(1H,s) 7.75(2H,d,J=8.3Hz), 7.88(1H,s), 8.02(2H,d,J=8.4Hz)

l) Preparation of (tert-Butoxycarbonylmethylamino)acetic acid 4-bromomethyl-2,6-dimethylphenyl ester

To a solution of 1.35g of 3,5-dimethyl-4-hydroxybenzaldehyde, 1.73g of N-(tert-butoxycarbonyl)sarcosine and 0.2g of 4-(N,N-dimethylamino)-pyridine in 20ml of dichloromethane was added 1.9g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and stirring was continued for 2.5h at room temperature. The mixture was diluted with ethyl acetate and was washed with 0.25N HCl. The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain 4-(tert-butoxycarbonylmethylamino)acetoxy-3,5-dimethylbenzaldehyde (2.9g) as a yellow oil.

A mixture of 2.88g of 4-(tert-butoxycarbonylmethylamino)acetoxy-3,5-dimethylbenzaldehyde and 0.34g of sodium borohydride in 25ml of tetrahydrofuran was stirred for 2h at room temperature. The mixture was diluted with ethyl acetate and was washed with 0.25N HCl. The organic layer was dried over anhydrous sodium sulfate and

concentrated to obtain (tert-butoxycarbonylmethylamino)acetic acid 2,6-dimethyl-4-hydroxymethylphenyl ester (2.9g) as a colourless syrup.

To a solution of 2.8g of (tert-butoxycarbonylmethylamino)acetic acid 2,6-dimethyl-4-hydroxymethylphenyl ester and 2.73g of triphenylphosphine in 30ml of dichloromethane, 3.44g of carbon tetrabromide was added and the mixture was stirred for 1h at room temperature. The mixture was concentrated and the residue was chromatographed on silica gel (Wakogel C-200, solvent : CH2Cl2)to obtain (tert-butoxycarbonylmethylamino)acetic acid 4-bromomethyl-2,6-dimethylphenyl ester (2.97g, 89%) as a colourless oil.

FAB-MS(+) : m/z 386 (MH)+

1H-NMR($CDCl_3$)

1.48(9H,s) 2.15(6H,s), 3.02(3H,s), 4.23(2H,br.d), 4.43(2H,s), 7.11(2H,br.s)

m) Preparation of (2R,3R)-4-[4- (N-tert-Butoxycarbonyl-N-methylaminoacetoxy)-3,5-dimethylbenzyl]-1-[3-[4-(4-cyano-phenyl)thiazol-2-yl]-2-hydroxy-2-(2,4,5-trifluorophenyl)butyl] - 1H-[1,2,4]triazol-4-ium bromide

A mixture of 140mg of (1R,2R)-4-[2-[2-hydroxy-1-methyl-3-[1,2,4]triazol-1-yl-2-(2,4,5-trifluorophenyl)propyl]thiazol-4-yl]benzonitrile and 131mg of (tert-butoxycarbonylmethylamino)acetic acid 4-bromomethyl-2,6-dimethylphenyl ester, prepared above, in 5mL of acetonitrile was stirred for 20h at reflux and concentrated. The residue was chromatographed on silica gel (Wakogel C-200, solvent : CH2Cl2 / MeOH=12 / 1) to obtain 178mg(69%) of (2R,3R)- 4-[4-(N-tert-butoxycarbonyl-N-methylaminoacetoxy)-3,5-dimethylbenzyl]-1-[3-[4-(4-cyanophenyl)thiazol-2-yl]-2-hydroxy-2-(2,4,5-trifluorophenyl)butyl] -1H-[1,2,4]triazol-4-ium bromide as a white solid.

FAB-MS(+) : m/z 761 (M)+

1H-NMR($CDCl_3$):

1.23(3H,d,J=7.5Hz), 1.47(9H,s) 2.14(6H,s), 3.02(3H,s),
4.10(1H,q,J=7.5Hz), 4.25(2H,s), 5.02(1H,d,J=14.2Hz),
5.14(1H,d,J=14.2Hz), 5.37-5.54(2H,m), 6.31(1H,s), 6.92-7.02(1H,m),
7.08(2H,br.d), 7.36-7.46(1H,m), 7.58(1H,br.s), 7.73(2H,d,J=8.4Hz),
8.01(1H,s), 8.05(2H,d,J=8.4Hz), 11.36(1H,s)

n) Preparation of 1-[(2R,3R)-3-[4-(4-Cyanophenyl)thiazol-2-yl]-2-hydroxy-2-(2,4,5-trifluorophenyl)butyl]-4-(3,5-dimethyl-4-methylaminoacetoxybenzyl)-1H-[1,2,4]triazol-4-ium bromide hydrochloride

A mixture of 167mg of (2R,3R)- 4-[4-(N-tert-butoxycarbonyl-N-methylaminoacetoxy)-3,5-dimethylbenzyl]-1-[3-[4-(4-cyanophenyl)-thiazol-2-yl]-2-hydroxy-2-(2,4,5-trifluorophenyl)butyl]-1H-[1,2,4]triazol-4-ium bromide and 2ml of 4N-HCl in ethyl acetate in 4ml of ethyl acetate was stirred for 4h at room temperature and filtered. The white solid was washed with ether and dried in vacuo to obtain 141mg(92%) of 1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-hydroxy-2-(2,4,5-trifluorophenyl)butyl]-4-(3,5-dimethyl-4-methylaminoacetoxybenzyl)-1H-[1,2,4]triazol-4-ium bromide hydrochloride.

FAB-MS(+) : m/z 661 (M)+

1H-NMR(DMSO-d6):

1.21(3H,d,J=7.3Hz), 2.11(6H,s), 2.64(3H,br.t), 4.12(1H,q,J=7.3Hz),
4.42(2H,br.t), 4.74(1H,d,J=14.2Hz), 5.02(1H,d,J=14.2Hz), 5.41(2H,s),
6.87(1H,s), 7.13(2H,s), 7.26-7.36(1H,m), 7.62-7.73(1H,m),
7.94(2H,d,J=8.6Hz), 8.21(2H,d,J=8.6Hz), 8.46(1H,s),
9.08(1H,s), 9.51(2H,br.s), 10.19(1H,s)

Example 4

a) Preparation of (2R)-2',5'-difluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-propiophenone

A mixture of magnesium (7.25 g, 0.298 mol) and iodine (catalytic amount) and1-bromo-2,5-difluorobenzene (20.0 g, 0.178 mol) in THF (250ml) was vigously stirred. The color of iodine was disappeared and the inner temperature rose up to 65°C. To this mixture was added additional 1-bromo-2,5-difluorobenzene (30.0 g, 0.267 mol) dropwise to maintain the inner temperature from 50 to 55°C over 45min. The resulting mixture was stirred at 55°C for 30min. then at r.t. for 1hr. The mixture was cooled down to -5°C. To this mixture was added a solution of 4-[(2R)-2-(3,4,5,6-Tetrahydro-2H-pyran-2-yloxy)propionyl] morpholine (52.5 g, 0.216 mol) in THF (150ml) dropwise over 40min. And the resulting mixture was stirred at r.t. for 4hrs. The reaction mixture was cooled down to 5°C and saturated NH4Cl aq. (100ml) was added carefully. The whole was diluted with H2O (600ml) and extracted with EtOAc (400ml + 200ml x 2). The combined organic layer was dried over Na2SO4 and concentrated in vacuo. The residue was chromatographed on silica gel (n-hexane : EtOAc = 10 :1 ~ 5 : 1) to give (2R)-2',5'-Difluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-propiophenone (47.3 g, 81 %) as pale yellow syrup.

Physical form : colorless oil ; FAB-MS : m/z 271$(M+H)^+$; ^{1}H-NMR(CDCl3) δ 1.42~1.90(9H,m),3.32~3.40(1Hx1/2,m),3.69~3.77(1Hx1/2,m),3.86~3.94(1Hx1/2,m),4.66(1Hx1/2,t,J=3.6Hz),4.75(1Hx1/2,t,J=3.6Hz),4.87(1Hx1/2,q,J=6.6Hz),5.11(1Hx1/2,q,J=6.9Hz),7.08~7.25(2H,m),7.49~7.55(1H,m).

b) Preparation of 2-(2,5-difluorophenyl)-2-[(1R)-1-(3,4,5,6,-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane

1) NaH (42.3 g, 60% in mineral oil, 1.06 mol), placed in a 3 L three-neck round bottle flask, was washed with hexane (100 mLx3) and dried in vacuo.

DMSO (500 mL, dried over 3A molcular sieves) was added under N_2 atmosphere and the resulting suspenion was cooled in an ice-water bath. Trimethylsulfoxonium iodide (275.2 g, 1.25 mol) was added portionwise over a period of 30 min (caution: addition of a large quantity of sulfoxonium iodide in one portion causes vigorous hydrogen gas evolution and temperature raising.). After stirring for half an hour at 0 °C, the mixture was allowed to warm to room temperature and stirred for 1 h. To the resulting viscous suspension was added dry THF (1 L), and the mixture was stirred for further 1 h at room temperature. A solution of (2R)-2',5'-Difluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-propiophenone (260 g, 0.962 mol) in dry THF (500 mL) was added *via* cannula over a period of 30 min and the mixture was stirred for 2 h at room temperature. Water (1 L) was added to quench the reaction and the mixture was extracted with AcOEt (500 mL x 3). AcOEt layer was combined and washed with brine (500 mL x 2), dried over $MgSO_4$ and evaporated *in vacuo* to give crude product. ^{1}H NMR spectrum indicated the diastereomeric ratio is ca. 6 : 1.

2) To a suspension of trimethylsulfoxonium iodide (147.5g, 670mmol) in anhydrous THF(600ml) was added n-BuLi (427ml, 1.57M in hexane, 670mmol) at 0°C dropwisely. After the addition was complete, the reaction mixture was warmed to room temperature, stirred for 30 minutes. The mixture was cooled to 0°C and DMPU (130ml) was added, followed by dropwise addition of (2R)-2',5'-Difluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-propiophenone (150g, 550mmol) from a droping funnel. The funnel was washed with THF (60ml). After the addition was complete, the reaction mixture was warmed to rom temperature and stirred overnight. The mixture was extracted with ethyl acetate/hexane (1/1), washed with water, brine. The combined organic phase was dried (Na_2SO_4), filtered, concentrated to give a residue. The residue was filtered through a short SiO_2 column (EtOAc/hexane = 1/10). The solvent was removed and the product was dried with high vacum pump overnight(98g, 63%, diastereoselectivity: 15:1).

Physical form : pale yellow syrup, EI-MS: m/z 284 $(M)^+$; ^{1}H-NMR(CDCl3) δ 1.15(3Hx1/2,dd,J=6.6,1.3Hz), 1.24(3Hx1/2,dd,J=6.6,1.3Hz),1.52~1.87(6H,m),2.83~2,90(1H,m),3.07(1Hx1/2,d,J=5.3Hz),3.36(1Hx1/2,d,J=5.6Hz),3.48~3.56(1H,m),3.82~3.92(1H,m),4.00~4.16(1H,m),4.73~4.92(1H,m),6.96~7.02(1H,m),7.09~7.15(1H,m).

c) Preparation of (2R,3R)-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol

1) To a suspension of NaH (38.5 g, 60% in mineral oil, 0.962 mol, washed with hexane three times) in DMF (1 L) cooled in an ice-bath was added triazole (133 g, 1.92 mol) portionwise over a period of 30 min. After completion of the addtion, the mixture was warmed to room temperature. The above crude 2-(2,5-Difluorophenyl)-2-[(1R)-1-(3,4,5,6,-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane was added and the mixture was heated at 70 °C for 8 h. After cooling to room temperature, the reaction mixture was quenched with water (1 L) and the mixture was extracted with EtOAc (1 L x 3). The EtOAc layer was combined and washed with water and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The portion of residue was chromatographed on silicagel for analysis (n-hexane : EtOAc = 4 : 1 ~ 1 : 5) to give pure (3R)-2-(2,5-difluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol.

Physical form : colorless syrup ; FAB-MS: m/z 354 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ

1.00(3Hx1/2,d,J=6.6Hz),1.13(3Hx1/2,d,J=6.6Hz),1.42~1.88(6H,m),3.38~3.60(1H,m),3.80~4.00(1H,m),4.32~5.02(5H,m),6.83~6.99(2H,m),7.14~7.21(1H,m),7.73(1Hx1/2,s),7.74(1Hx1/2,s),7.92(1Hx1/2,s),7.95(1Hx1/2,s).

2) The crude residue without purification was dissolved in MeOH (250 mL) and hexane (1 L) and 0.5 N aqueous HCl solution (1 L) were added (please make sure the aqueous phase is acidic). The mixture was stirred for 2 h at room temperature (the solution became clear two phases). The organic layer was removed and the aqueous layer was washed with hexane (500 mL x 2), and combined hexane layer was extracted with water (500 mL). Aqueous phases were combined and basified by adding solid Na_2CO_3 (26 g) with cooling in an ice-bath. The resulting heterogeneous mixture was extracted with EtOAc (1 L x 3) and conbined EtOAc layer was washed with brine (500 mL x 2), dried over $MgSO_4$ and evaporated under reduced pressure. The obtaining residue was purified by silica gel column chromatography (eluent: CH_2Cl_2 only to CH_2Cl_2/EtOH = 20/1). Fractions containing the desired diastereoisomer as the major were combined and evaporated under reduced pressure to give crude product (159 g). The product was dissolved in refluxing t-BuOMe (700 mL). Insoluble white powdery crystal

(heterodimer) was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting solid was recrystalized from t-BuOMe-hexane to give pure (2R,3R)-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol (110 g, 42% over 3 steps).

Physical form : colorless syrup ; FAB-MS: m/z 270 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 0.99(3H,d,J=6.6Hz),2.61(1H,d,J=10.6Hz),4.31~4.36(1H,m),4.79,4.88(2H,ABq,J=14.5Hz),4.84(1H,s),6.84~6.99(2H,m),7.13~7.19(1H,m),7.84(1H,s),7.85(1H,s).

d) Preparation of (2R,3S)-2-(2,5-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)-methyl]-oxirane

To a solution of (2R,3R)-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol (53.0 g, 197 mmol) and Et_3N (54.8 mL, 394 mmol) in CH_2Cl_2-EtOAc (1 :3, 400 mL) cooled in an ice-bath was added MsCl (17.5 mL, 227 mmol) dropwise over a period of 15 min. After stirring for 30 min at 0 °C, the mixture was warmed to room temperature and quenched with water (200 mL). EtOAc (200 mL) was added and the organic layer was washed with water and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The obtaining residue was dissolved in MeOH (500 mL) and cooled in an ice-bath. A solution of NaOMe (41.8 g, 28% in MeOH, 217 mmol) was added dropwise and after the completion of the addition, the mixture was stirred for 15 min at 0 °C. MeOH was evaporated under reduced pressure and the resulting residue was dissolved in EtOAc (500 mL). The EtOAc solution was washed with water and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The obtaining solid was recrystalized from t-BuOMe-hexane to give pure (2R,3S)-2-(2,5-Difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)-methyl]-oxirane (43.5 g, 88%).

Physical form : white solid ; FAB-MS : m/z 252 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.64(3H,d,J=5.6Hz),3.19(1H,q,J=5.6Hz),4.42,4.97(2H,ABq,J=14.8Hz),6.75~6.81(1H,m),6.89~7.01(2H,m),7.83(1H,s),7.98(1H,s).

e) Preparation of (2S,3R)-3-(2,5-difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyronitrile

To a solution of acetone cyanohydrin (61.0 mL, 600 mmol) in dry THF (500 mL) cooled in an ice-bath was added LiH (4.77 g, 600 mmol) portionwise. After stirring for 1 h at 0 °C, the mixture was warmed to room temperature and stirred further for 1 h. (2R,3S)-2-(2,5-Difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)-methyl]-oxirane (50.0 g, 199 mmol) was added and the mixture was heated to reflux for 4 h. After approx. 300 mL of THF was distilled out under atmospheric pressure, the mixture was cooled in an ice-bath and quenched with water (250 mL). The mixture was extracted with EtOAc (600 mL) and the EtOAc layer was washed with water (200 mL x 4) and brine (200 mL x 2), dried over $MgSO_4$ and evaporated. The obtaining solid was recrystalized from isopropanol-hexane to give pure (2S,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyronitrile (45.9 g, 83%).

Physical form : colorless syrup ; FAB-MS : m/z 279 $(M+H)^+$; ^{1}H-NMR(CDCl3)

δ 1.19(3H,d,J=7.3Hz),3.33(1H,q,J=7.3Hz),4.82,5.00(2H,ABq,J=13.9Hz),5.56(1H,brs),6.89~7.04(2H,m),7.12~7.19(1H,m),7.85(1H,s),7.86(1H,s).

f) Preparation of (2R,3R)-3-(2,5-difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-ylthiobutyramide

(2S,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyronitrile (50.0 g, 180 mmol), diethyl dithiophosphate (134 mL, 719 mmol), isopropanol (50 mL) and water (40 mL) were mixed together and the mixture was heated in an oil-bath (temp. setting at 110 °C) for 3 h. After cooling to 0 °C, 5% Na_2CO_3 aqueous solution (500 mL) was added slowly and then solid Na_2CO_3 (25 g) was added portionwise. The mixture was extracted with EtOAc (1 L) and the EtOAc layer was washed with sat. $NaHCO_3$ aqueous solution, water (x 2) and brine, dried over $MgSO_4$ and evaporated under reduce pressure. The resulting solid was purified by recrystalization from isopropanol to give pure (2R,3R)-3-(2,5-

difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-ylthiobutyramide (47.9 g, 85%).

Physical form : White solid ; FAB-MS : m/z 313 $(M+H)^+$; ^{1}H-NMR($CDCl_3$) δ 1.12(3H,d,J=7.3Hz),3.74(1H,q,J=7.3Hz),4.55,5.12(2H,ABq,J=14.5Hz),5.84 (1H,s),6.85~7.02(2H,m),7.15~7.22(1H,m),7.80(1H,s),7.89(1H,s),7.89(1H,brs),8.43 (1H,brs).

g) Preparation of 2-bromo-4'-cyanoacetophenone

To a mixture of para-cyanoacetophenone (52g, 0.36mol) in chloroform (520ml) and 48%HBr (5.2ml), a solution of bromine (19.3ml) in chloroform (52ml) was added dropwise over a period of 20min. The mixture was stirred for 3h at room temperature and neutralized to pH7 with sat. NaHCO3. The organic layer was washed with sat. NaCl and dried over anhydrous Na2SO4 and concentrated. The residue was chromatographed on silica gel (AcOEt / n-hexane = 1 / 3 as an eluent) and recrystallized to obtain 2-bromo-4'-cyanoacetophenone as a colourless plate (23.4g, 29%).

EI-MS(+) : m/z 223 (M+)
1H-NMR(CDCl3)
δ4.43(2H,s), 7.80(2H,d,J=6.6Hz), 8.09(2H,d,J=6.6Hz)

h) Preparation of (2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol

To a solution of (2R,3R)-3-(2,5-difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-ylthiobutyramide (106 g, 340 mmol) in EtOH (500 mL) warmed at 50 °C in a water-bath was added 4-cyano-2'-bromoacetophenone (78.4 g, 350 mmol) portionwise over a period of 15 min and the mixture was stirred for 2 h at 50 °C. After evaporation of EtOH under reduced pressure, the residue was dissolved in EtOAc (1.2 L) and the solution was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography followed by trituration with t-BuOMe to give pure (2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl)-1-(1H-

1,2,4-triazol-1-yl)-butan-2-ol (117 g, 79%) as a white powdery crystal.

Physical form : colorless heavy syrup ; ESI-MS : m/z 437 $(M)^+$; ^{1}H-NMR($CDCl_3$) δ 1.25(3H,d,J=7.3Hz),4.12(1H,q,J=7.3Hz),4.26,4.96(2H,ABq,J=14.5Hz),5.75(1H,s),6.89~7.07(2H,m),7.23~7.29(1H,m),7.65(1H,s),7.71(1H,s),7.75,8.02(4H,ABq,J=8.6Hz),7.85(1H,s).

Example 5

a) Preparation of (2R)-2', 4', 5'-trifluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy) propiophenone

A mixture of magnesium (turnings, 228mg, 1.2eq) and 1-bromo-2,4,5-trifluorobenzene (1.1 ml, 1.2eq) in dry tetrahydrofuran (25 ml) was vigorously stirred for 3h at room temperature until magnesium was completely dissolved. After the mixture was cooled to -10 °C, a solution of 4-[(2R)-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)propinyl]morpholine (1.9g) in dry tetrahydrofuran (5ml) was added dropwise over a period of 5 min. The whole was stirred at r.t. for 24 h. A saturated aqueous solution of ammonium chloride and water were added to the reaction mixture and the resulting mixture was extracted with ethyl acetate. The extracts were combined, washed successively with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure followed by purification of the residue by silica gel chromatography (using n-hexane:ethyl acetate = 30:1 ~ 5 : 1 as an eluent) gave (2R)-2',4',5'-trifluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy) propiophenone (1.8g, 80% yield) as a pale yellow oil. The product was a mixture of 2 diastereomers.

ESI-MS(+) : m/z 289 (MH)+
1H-NMR(CDCl3)
δ1.42-1.90(9H,m), 3.31-3.93(2H,m), 4.62-5.12(2H,m), 6.95-7.05(1H,m), 6.68-7.78(1H,m)

b) Preparation of 2-(2,4,5-trifluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane

Trimethylsulfoxonium iodide (697mg, 1.2 eq) was added portionwise to a stirred mixture of sodium hydride [60 % mineral oil dispersion] (122mg, 1.15 eq) and dry dimethyl sulfoxide (7ml) at 0 °C. The resulting mixture was stirred at room temperature for 40 min and then cooled in an ice bath. A solution of (2R)-2',4',5'-trifluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)propiophenone (760mg) in dry dimethyl sulfoxide (2 ml) was added to the mixture and stirring was continued for 2 h at room temperature. The mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed successively with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 2-(2,4,5-trifluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane (810mg) as a pale yellow oil, which was a mixture of 4 diastereomers and was used for the next step without further purification.

c) Preparation of (3R)-2-(2,4,5-trifluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol

1H-1,2,4-Triazole (510mg) was added portionwise to a mixture of sodium hydride [60 % mineral oil dispersion] (264mg) and dry N,N-dimethylformamide (8ml) and the mixture was stirred at room temperature for 35 min. A solution of 2-(2,4,5-trifluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane (796mg) obtained above in dry N,N-dimethylformamide (2ml) was added to the mixture at room temperature. The resulting mixture was heated at 80 °C for 1.5hr. with stirring and after being cooled, the mixture was poured into ice-water and the whole was extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated off under reduced pressure and purification of the residue by silica gel chromatography (using n-hexane : ethyl acetate = 1 : 2 as an eluent) gave (3R)-2-(2,4,5-trifluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol (760mg, 78 % yield for 2 steps) as a colourless oil. The product was a mixture of 4 diastereomers.

ESI-MS(+) : m/z 372 (MH)+
1H-NMR(CDCl3)

δ1.00-1.35(3H,m), 1.40-1.92(6H,m), 3.39-5.00(7H,m), 6.79-6.91(1H,m), 7.27-7.38(1H,m), 7.74-8.12(2H,m)

d) Preparation of (2R,3R)-2-(2,4,5-trifluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol

A mixture of (3R)-2-(2,4,5-trifluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol (740mg) and pyridinium p-toluene sulfonate (PPTS) 200mg in ethanol (15 ml) was heated at 55 °C for 7h. The reaction mixture was partitioned between ethyl acetate and water. The water layer was extracted with ethyl acetate.The combined organic extracts were dried over anhydrous magnesium sulfate, and concentrated to dryness in vacuo. Purification of the residue by silica gel chromatography (using dichloromethane : methanol = 20 : 1 as an eluent) gave (2R,3R)-2-(2,4,5-trifluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol (361mg, 63 %) as white amorphous.

ESI-MS(+) : m/z 288 (MH)+
1H-NMR(CDCl3)
δ0.99(3H,d,J=6.6Hz), 2.45(1H,br.d), 4.30(1H,m), 4.80(1H,d,J=14.2Hz), 4.84(1H,d,J=14.2Hz), 4.88(1H,s), 6.83-6.93(1H,m), 7.29-7.36(1H,m), 7.87(1H,s), 7.88(1H,s)

c) Preparation of (2R,3S)-2-(2,4,5-trifluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane

Methanesulfonyl chloride (0.11ml, 1.1 eq) was added to a mixture of (2R,3R)-2-(2,4,5-trifluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol (345mg) and triethylamine (0.2ml) in dry ethyl acetate (2ml) and dry dichloromethane (9 ml) at 0 °C. The mixture was stirred at room temperature for 2h and the reaction mixture was quenched with saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous sodium sulfate, and evaporation of the solvent under reduced pressure gave the mesylate as an oil. The resulting oil was dissolved in methanol (10 ml) and sodium methoxide [28 % in methanol] (0.29ml) was added to the mixture at 0 °C. The mixture was stirred at 0 °C for 30 min and was partitioned between ethyl acetate and water. The organic extract was dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent and purification of the residue by silica gel chromatography (using

dichloromethane : methanol = 40 : 1 as an eluent) gave (2R,3S)-2-(2,4,5-trifluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane (310mg, 96%) as a white solid.

ESI-MS(+) : m/z 270 (MH)+
1H-NMR(CDCl3)
δ1.64(3H,d,J=5.6Hz), 3.19(1H,q,J=5.6Hz), 4.40(1H,d,J=14.5Hz), 4.93(1H,d,J=14.5Hz), 6.85-6.95(2H,m), 7.83(1H,s), 8.02(1H,s)

f) Preparation of (2S,3R)-3-(2,4,5-trifluorophenyl)-3-hydroxy-2-methyl-4-(1H-1,2,4-triazol-1-yl)butyronitrile

A mixture of 295mg of (2R,3S)-2-(2,4,5-trifluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane, 0.59ml of trimethylsilylcyanide and 222mg of magnesium oxide (light) in 10ml of o-xylene was stirred at 130 °C for 23h. After cooling the mixture was filtered and the filtrate was concentrated to dryness. The resulting oil was dissolved in 10ml of THF and 0.39ml of conc.hydrogen chloride was added to the mixture. The mixture was stirred at room temperature for 22h and was diluted with ethyl acetate and aqueous sodium bicarbonate. The organic extract was dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel chromatography (using dichloromethane : methanol = 30 : 1 as an eluent) gave (2S,3R)-3-(2,4,5-trifluorophenyl)-3-hydroxy-2-methyl-4-(1H-1,2,4-triazol-1-yl)butyronitrile (243mg, 75%) as a white solid.

ESI-MS(+) : m/z 297 (MH)+
1H-NMR(CDCl3)
δ1.19(3H,d,J=7.3Hz), 3.27(1H,q,J=7.3Hz), 4.82(1H,d,J=14.2Hz), 4.96(1H,d,J=14.2Hz), 5.60(1H,s), 6.85-6.95(1H,m), 7.29-7.37(1H,m), 7.87(1H,s), 7.88(1H,s)

g) Preparation of (2R,3R)-3-(2,4,5-trifluorophenyl)-3-hydroxy-2-methyl-4-1H-[1,2,4]triazol-1-yl)thiobutyramide

A mixture of 235mg of (2S,3R)-3-(2,4,5-trifluorophenyl)-3-hydrxy-2-methyl-4-(1H-1,2,4-triazol-1-yl)butyronitrile in 1.5ml of dithiophosphoric acid O,O-diethyl ester and 0.5ml of water was stirred at 100 °C for 30min. After cooling, the mixture was washed with n-hexane and the residue was diluted with ethyl

acetate and aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel column chromatography (using dichloromethane : methanol = 12 : 1 as an eluent) gave (2R,3R)-3-(2,4,5-trifluorophenyl)-3-hydroxy-2-methyl-4-1H-[1,2,4]triazol-1-yl)thiobutyramide (255mg, 98%) as a white amorphous.

ESI-MS(+) : m/z 331 (MH)+
1H-NMR(CDCl3)
δ1.13(3H,d,J=7.3Hz), 3.71(1H,q,J=7.3Hz), 4.54(1H,d,J=14.5Hz), 5.06(1H,d,J=14.5Hz), 5.92(1H,s), 6.83-6.91(1H,m), 7.29-7.38(1H,m), 7.67(1H,br.s), 7.82(1H,s), 7.88(1H,s), 8.30(1H,br.s)

h) Preparation of (2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-1-(1H-1,2,4-triazol-1-yl)-2-(2,4,5-trifluorophenyl)-butan-2-ol

A mixture of 188mg of (2R,3R)-3-(2,4,5-trifluorophenyl)-3-hydroxy-2-methyl-4-1H-[1,2,4]triazol-1-yl)thiobutyramide and 141mg of 2-bromo-4'-cyanoacetophenone in 4ml of acetonitrile was stirred for 22h at room temperature. The mixture was diluted with ethyl acetate and was washed with aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate and concentrated. Purification of the residue by silica gel column chromatography (using dichloromethane : ethyl acetate = 3 : 1 as an eluent) gave (2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-1-(1H-1,2,4-triazol-1-yl)-2-(2,4,5-trifluorophenyl)-butan-2-ol
(212mg, 82%) as a white solid.

ESI-MS(+) : m/z 456 (MH)+
1H-NMR(CDCl3)
δ1.25(3H,d,J=7.3Hz), 4.08(1H,q,J=7.3Hz), 4.25(1H,d,J=14.2Hz), 4.91(1H,d,J=14.2Hz), 5.88(1H,s), 6.89-6.99(1H,m), 7.35-7.45(1H,m), 7.65(1H,s), 7.71(1H,s) 7.75(2H,d,J=8.3Hz), 7.88(1H,s), 8.02(2H,d,J=8.4Hz)

Example 6

Preparation of (2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(3-fluorophenyl)-1-(1H-1,2,4-triazole-1-yl)-butan-2-ol

This compound was synthesized by the same procedure as that of Example 4 or 5.

FAB-MS(+) : m/z 420 (M)+
1H-NMR(CDCl3)
δ1.28(3H,d,J=7.3Hz), 3.85(1H,q,J=7.3Hz), 4.31(1H,d,J=14.2Hz), 4.56(1H,d,J=14.2Hz), 5.78(1H,s), 6.92-7.60(4H,m), 7.62-7.72(3H,m), 7.75(2H,d,J=8.6Hz), 8.01(2H,d,J=8.6Hz)

Example 7

Preparation of (2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(3,4-difluorophenyl)-1-(1H-1,2,4-triazole-1-yl)-butan-2-ol

This compound was synthesized by the same procedure as that of Example 4 or 5.

FAB-MS(+) : m/z 437 (M)+
1H-NMR(CDCl3)
δ 1.28(3H,d,J=6.9Hz),3.83(1H,q,J=6.9Hz),4.30,4.55(2H,ABq,J=14.4Hz),5.89 (1H,s),6.96~7.00(1H,m),7.06~7.12(1H,m),7.18~7.27(1H,m),7.63(1H,s),7.78(1H,s), 7.79(1H,s),7.75,8.01(4H,ABq,J=8.4Hz)

Example A:

Dry ampoules for intramuscular administration:

A lyophilizate of 0.5 g 1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methyl-amino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium chloride hydrochloric acid

salt is prepared in the usual manner and filled into an ampoule. Prior to the administration the lyophilizate is treated with 2.5 ml of a 2% aqueous lidocaine hydrochloride solution.

Example B:

Hard gelatin capsules each containing the following ingredients were manufactured in the conventional manner *per se*:

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium chloride hydrochloric acid salt	100 mg
Lactose	56 mg
Crystalline Cellulose	30 mg
Silicic acid, Light Anhydrous	10 mg
Talc	3 mg
Magnesium stearate	1 mg
Total	200 mg

Example C:

Tablets each containing the following ingredients were manufactured in the conventional manner *per se*:

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium chloride hydrochloric acid salt,	100 mg

Lactose	60 mg
Corn starch	20 mg
Sodium Starch Glycolate	10 mg
Polyvinylpyrrolidone	6 mg
Talc	3 mg
Magnesium stearate	1 mg
	Total 200 mg

Example D:

Hard gelatin capsules each containing the following ingredients were manufactured in the conventional manner *per se*:

(2R,3R)-3-[4-(4-Cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol,	100 mg
Lactose	56 mg
Crystalline cellulose	30 mg
Silicic acid, light anhydrous	10 mg
Talc	3 mg
Magnesium stearate	1 mg
	Total 200 mg

Example E:

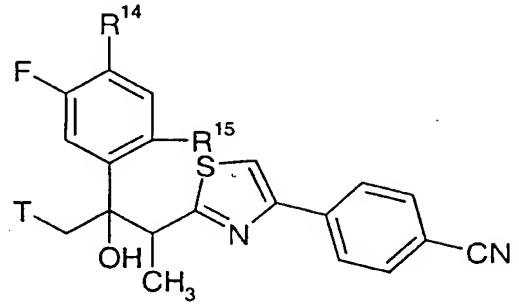
Tablets each containing the following ingredients were manufactured in the conventional manner *per se*:

(2R,3R)-3-[4-(4-Cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl) -1-(1H-1,2,4-triazol-1-yl)-butan-2-ol,	100 mg
Lactose	60 mg
Corn starch	20 mg
Sodium starch glycolate	10 mg
Polyvinylpyrrolidone	6 mg

Talc	3 mg
Magnesium stearate	1 mg
	Total 200 mg

Claims

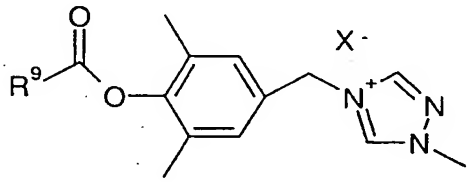
1. Azole derivatives of the formula I



I

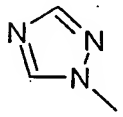
wherein R^{14}, R^{15} are each independently hydrogen or fluorine,

T is a group of the formula:



(T^1)

or



(T^2)

wherein

R^9 is pyrrolidinyl or a group A-NH-B-,

A is hydrogen or straight-chain or branched C_1-C_5 alkyl;

B is straight-chain or branched C_1-C_4 alkylene,

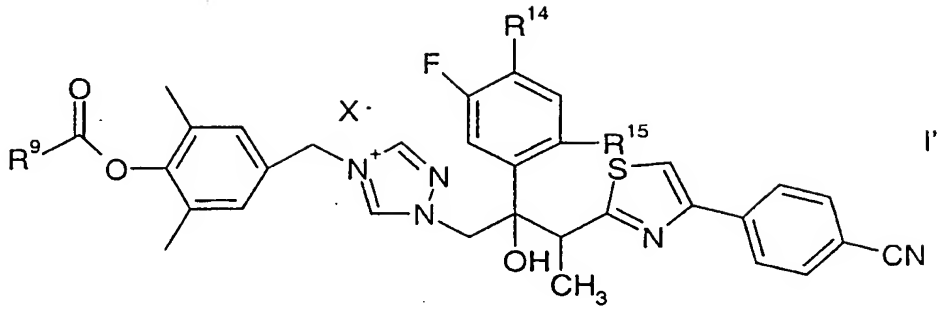
$-CH_2-CONH-CH_2$ or $-CH_2CH_2CH_2-CH(NH_2)$; and

X^- is a pharmaceutically acceptable anion;

and pharmaceutically acceptable salts of said compounds, and hydrates and solvates of the compounds of formula I and the salts thereof.

2. Azoles as in claim 1 wherein T is the group T^1, i.e. azoles of

the formula I'



I'

wherein R^9, R^{14} and R^{15} are as in claim 1.

3. A compound as in claim 1 or 2, wherein R^9 is pyrrolidinyl, aminomethyl, methylaminomethyl or ethylaminomethyl, and/or wherein $R^{14} = R^{15} = H$ or F, or R^{14} is H and R^{15} is F, and/or wherein X^- is Br^- or Cl^-, or a salt thereof, particularly the hydrobromide, hydrochloride or trifluoroacetate.

4. Azoles as in claim 1 or 2 selected from the following:

1-[(2R,3R)-3-[4-(4-cyanophenyl)-thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[(S)-3,5-dimethyl-4-(pyrrolidine-2-carbonyloxy)-benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)-thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[(S)-3,5-dimethyl-4-(pyrrolidine-2-carbonyloxy)-benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)-thiazol-2-yl)]-2-(3-fluorophenyl)-2-hydroxybutyl]-4-[(S)-3,5-dimethyl-4-(pyrrolidine-2-carbonyloxy)-benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

(2R,3R)-4-(4-aminoacetoxy-3,5-dimethylbenzyl)-1-[3-[4-(4-

cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

(2R,3R)-4-(4-aminoacetoxy-3,5-dimethylbenzyl)-1-[3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

(2R,3R)-4-(4-aminoacetoxy-3,5-dimethylbenzyl)-1-[3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)-acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]-benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

(2R,3R)-1-[3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[4-[(ethylamino)-acetoxy]-3,5-dimethylbenzyl]-1H- [1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

(2R,3R)-1-[3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[4-[(ethylamino)-acetoxy]-3,5-dimethylbenzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(ethylamino)-acetoxy]-benzyl]-1H-[1,2,4]triazol-4-ium bromide, and particularly its trifluoroacetic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)-acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium chloride, and particularly its hydrochloric acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)-acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium chloride, and particularly its hydrochloric acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium chloride, and particularly its hydrochloric acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]-benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrobromic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]-benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrobromic acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrobromic acid salt,

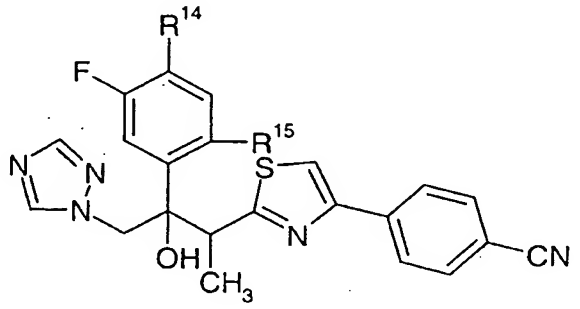
1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,4,5-trifluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)-acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrochloric acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(2,5-difluorophenyl)-2-hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]-benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrochloric acid salt,

1-[(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl]-2-(3-fluorophenyl)-2-

hydroxybutyl]-4-[3,5-dimethyl-4-[(methylamino)acetoxy]benzyl]-1H-[1,2,4]triazol-4-ium bromide hydrochloric acid salt.

5. Azoles as in claim 1 wherein T is the group T^2, i.e. azoles of the formula II



II

wherein R^{14} and R^{15} are as in claim 1.

6. A compound as in claim 1, 3 or 5, wherein R^{14}=R^{15}=H or F, or R^{14} is H and R^{15} is F.

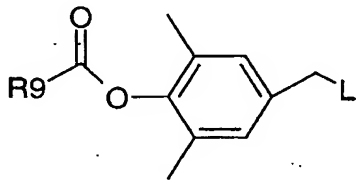
7. The compound of claim 1, 3 or 5 selected from the following triazoles:
(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-1-(1H-1,2,4-triazol-1-yl)-2-(2,4,5-trifluorophenyl) -butan-2-ol,
(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol,
(2R,3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(3-fluorophenyl)-1-(1H-1,2,4-triazole-1-yl)-butan-2-ol.

8. The compound selected from following intermediates:
(2R)-2',5'-Difluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-propiophenone,
2-(2,5-Difluorophenyl)-2-[(1R)-1-(3,4,5,6,-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane,
(3R)-2-(2,5-difluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol,
(2R,3R)-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol,
(2R,3S)-2-(2,5-Difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)-methyl]-

oxirane,
(2S,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-yl-butyronitrile,
(2R,3R)-3-(2,5-Difluoro-phenyl)-3-hydroxy-2-methyl-4-[1,2,4]triazol-1-ylthiobutyramide,
(2R)-2',4',5'-Trifluoro-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy) propiophenone,
2-(2,4,5-trifluorophenyl)-2-[(1R)-1-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)ethyl]oxirane,
(3R)-2-(2,4,5-trifluorophenyl)-3-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)-1-(1H-1,2,4-triazol-1-yl)-2-butanol,
(2R,3R)-2-(2,4,5-trifluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-2,3-butanediol,
(2R,3S)-2-(2,4,5-trifluorophenyl)-3-methyl-2-(1H-1,2,4-triazol-1-yl)methyloxirane,
(2S,3R)-3-(2,4,5-trifluorophenyl)-3-hydroxy-2-methyl-4-(1H-1,2,4-triazol-1-yl)butyronitrile or
(2R,3R)-3-(2,4,5-trifluorophenyl)-3-hydroxy-2-methyl-4-1H-[1,2,4]triazol-1-yl)thiobutyramide.

9. An antifungal composition comprising a compound as defined in any one of claim 1 to 7 and a carrier.

10. A process for the manufacture of an azole of formula I' as in claim 2, which process comprises reacting an azole compound of the general formula II as in claim 5, with a compound of the general formula (III),



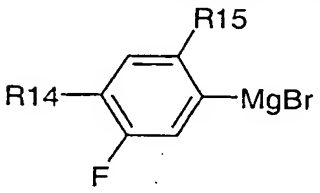
(III)

wherein R^9 is the same as defined in claim 1; and an amino group present in R^9 may be in protected form, and L is a leaving group,

followed if necessary by removal of a protecting group and/or if desired by salt formation.

11. A process for the manufacture of an azole of formula II as in claim 5, having the 2R,3R configuration, which process comprises:

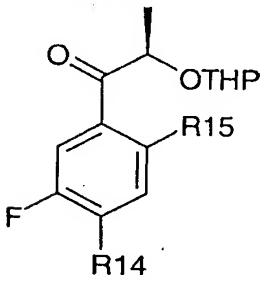
(a) reacting 4-[(2R)-2-(3,4,5,6-tetrahydro-2H-pyran-2-yloxy)propionyl] morpholine with a compound of the formula (1),



(1)

wherein R^{14} and R^{15} are the same as defined above,
followed by

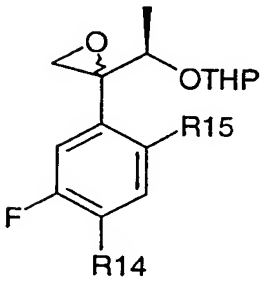
(b) reacting a compound of the formula (2),



(2)

wherein R^{14} and R^{15} are the same as defined above,
with trimethyl sulfoxonium iodide ,
followed by

(c) reacting a compound of the formula (3),



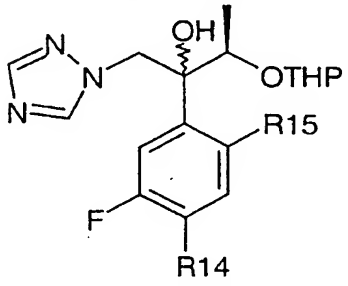
(3)

in which R^{14} and R^{15} are the same as defined above,

with triazole in the presence of sodium hydride,

followed by

(d) reacting a compound of the formula (4)



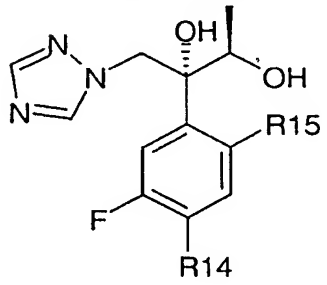
(4)

wherein R^{14} and R^{15} are the same as defined above,

with aqueous hydrochloric acid solution or pyridinium p-toluenesulfonate,

followed by

(e) reacting a compound of the formula (5),



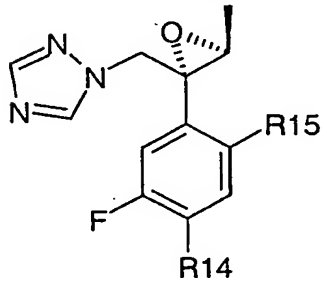
(5)

wherein R^{14} and R^{15} are the same as defined above,

with mesyl chloride in the presence of an organic base, then with sodium methoxide,

followed by

(f) reacting a compound of the formula (6)



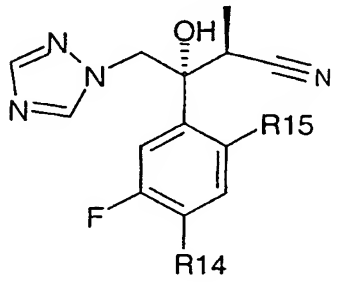
(6)

wherein R^{14} and R^{15} are the same as defined above,

with acetone cyanohydrin in the presence of lithium hydride or trimetylsilyl

cyanide in the presence of magnesium oxide,
followed by

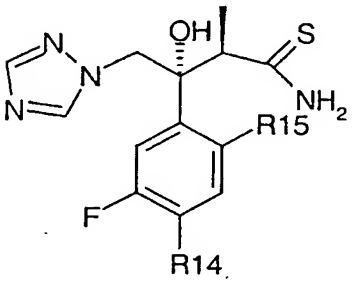
(g) reacting a compound of the formula (7),



(7)

wherein R^{14} and R^{15} are the same as defined above,
with dithiophosphoric acid O,O-diethyl ester,
followed by

(h) reacting a compound of the formula (8),



(8)

wherein R^{14} and R^{15} are the same as defined above,
with 2-bromo-4'-cyanoacetophenone.

12. The compounds of any one of claims 1 to 8, whenever prepared by the process of claim 10 or 11 or by an obvious chemical equivalent thereof.

13. The compounds of any one of claims 1 to 7 for use in medical therapy, particularly in the treatment of fungal infections and mycoses.

14. The use of a compound as defined in any one of claim 1 to 7 for the production of a medicament for the treatment of fungal infections and mycoses.

15. The novel compounds, compositions and uses as described hereinbefore, particularly with reference to the Example.

16. A method of the therapy of fungal infections and mycoses comprising administering to the infected organism an effective amount of a compound as defined in any one of claim 1 to 7.

***

INTERNATIONAL SEARCH REPORT

Inte 'onal Application No
PCT/EP 99/01327

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D417/06 A61K31/41 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 667 346 A (EISAI CO LTD) 16 August 1995 (1995-08-16) see the whole document; in particular, page 76; example 88	1-16
Y	WO 92 17474 A (PFIZER LTD ;PFIZER (US)) 15 October 1992 (1992-10-15) page 59; claim 1	1-16
Y	AU 45364 97 A (HOFFMANN LA ROCHE) 5 February 1998 (1998-02-05) the whole document	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 1999	17.08.99
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Fink, D

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/01327

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 16
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 99/01327

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0667346 A	16-08-1995	JP 7223950 A	22-08-1995
		JP 8020578 A	23-01-1996
		JP 8053426 A	27-02-1996
		JP 8165263 A	25-06-1996
		AU 696640 B	17-09-1998
		AU 1155695 A	17-08-1995
		AU 3931697 A	29-01-1998
		AU 7859298 A	01-10-1998
		CA 2141731 A	08-08-1995
		CN 1113241 A	13-12-1995
		FI 950514 A	08-08-1995
		HU 74098 A	28-11-1996
		NO 950425 A	08-08-1995
		NO 975774 A	08-12-1997
		NO 975775 A	08-12-1997
		NO 991165 A	08-08-1995
		NZ 270418 A	22-09-1997
		NZ 314252 A	24-10-1997
		NZ 314253 A	22-08-1997
		US 5648372 A	15-07-1997
		US 5792781 A	11-08-1998
		US 5789429 A	04-08-1998
		ZA 9500962 A	21-12-1995
WO 9217474 A	15-10-1992	PT 100331 A	31-08-1993
AU 4536497 A	05-02-1998	AU 3685097 A	12-03-1998
		CA 2214669 A	09-03-1998
		CN 1182739 A	27-05-1998
		CZ 9702828 A	17-06-1998
		EP 0829478 A	18-03-1998
		HR 970479 A	31-08-1998
		HU 9701479 A	01-02-1999
		JP 10114758 A	06-05-1998
		NO 974125 A	10-03-1998
		PL 322014 A	16-03-1998
		US 5900486 A	04-05-1999